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# CANADIAN PATENT

(54) PROCESS FOR PREPARING HEXAHYDROBENZO [6,7] CYCLOHEPTA[1,2,3-de] ISOQUINOLINES

(70) Humber, Leslie G.; Chou, Chih H.; Davis, Martin A.; Georgiadis, Minas P. and Bruderlein, Francois T., Canada

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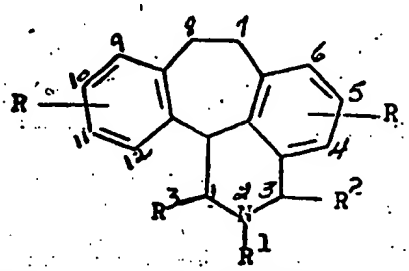
# PROCESS FOR PREPARING HEXAHYDROBENZO[6,7]CYCLOHEPTA[1,2,3-d,e]-ISOQUINOLINES


## Abstract of Disclosure

Process for preparing hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinolines from known 10,11-dihydro-dibenzo-cyclohepten-5-ones. The compounds are useful as antibacterial agents and as central nervous system depressants.

This invention relates to a process for preparing hexahydrobenz[6,7]cyclohepta[1,2,3-d,e]isoquinolines of the formula I



I.

in which R represents one or more substituents, either the same or different from each other, and selected from the group consisting of hydrogen, lower alkyl, halogen, hydroxyl, lower alkoxy, lower acyloxy, lower alkylthio, lower alkylsulfonyl, trihalomethyl, amino, lower alkylamino, di-(lower alkyl)aminosulfonyl, and nitro; $R^1$ is selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl and phenylalkyl and $R^2$ is selected from the group consisting of hydrogen, alkyl, alkenyl, (lower alkoxy)alkyl, cycloalkyl, cycloalkylalkyl, phenyl, and phenylalkyl, and $R^3$ is hydrogen or lower alkyl; and their pharmaceutically acceptable salts.

In the above passage the word "lower" means that the chemical group so designated contains from 1-4 carbon atoms.

Some of the compounds of this invention have been described in U.S. Patent 3,403,157, issued September 24, 1968. The compounds of this invention of formula I are useful as antibacterial agents. When tested, for example, by a modification of the method described by Grove and Randall in "Assay Methods of Antibiotics", Medical Encyclopedia, Inc. New York 1955, they have been found to be active against Staphylococcus pyogenes (both penicillin-sensitive and penicillin-resistant strains), Sarcina lutea, Strepococcus fecalis, and Escherichia coli. As antibacterial agents for topical use the compounds of Formula I, may be formulated as solutions, creams, or lotions with pharmacologically acceptable vehicles containing from 0.1 to 1.0 percent of the active ingredient. Such formulations may be applied topically to the site of infection as required.

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The useful central nervous system depressant activity of the hexahydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinolines of formula I and their acid addition salts with pharmaceutically acceptable acids may be demonstrated in standard pharmacologic tests, such as, for example, the tests described by R.A. Turner in "Screening Methods in Pharmacology", Academic Press, New York and London, 1965, pp. 69-99.

When the hexahydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinolines of this invention are used as central nervous system depressants in warm-blooded mammals, e. g. rats and mice, they may be used alone or in combination with pharmacologically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For example, they may be administered orally in solid form containing such excipients as starch, milk sugar, certain types of clay and so forth. They may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration they may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The dosage of the compounds of this invention will vary with the form of administration and the particular

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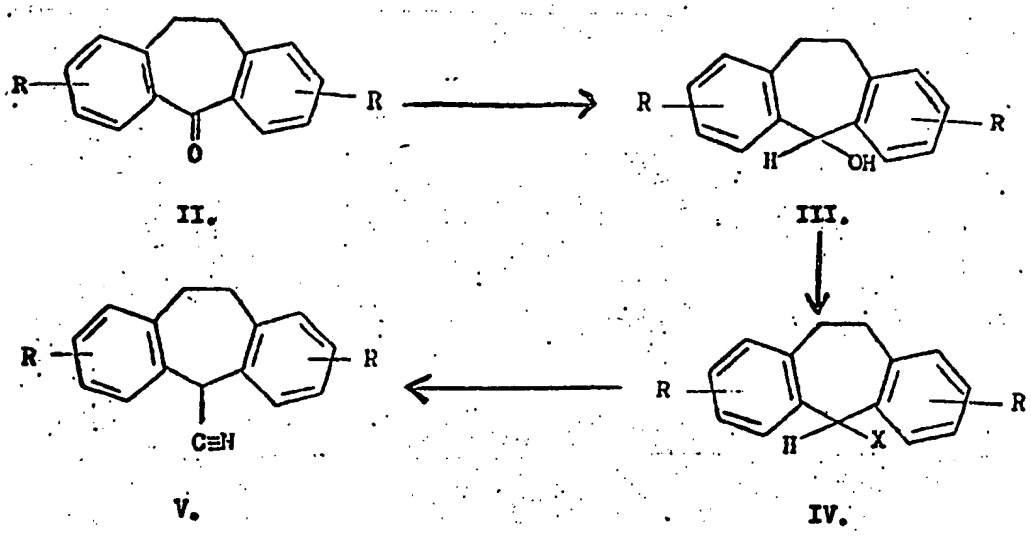
compound chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects and preferably at a level that is in a range of from about 1.0 mg to about 500 mg per kilo per day, although as aforementioned variations will occur. However, a dosage level that is in the range of from about 10 mg to about 100 mg per kilo per day is most desirably employed in order to achieve effective results.

The starting material of the formula II in which R represents hydrogen, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one, is described in J. Am. Chem. Soc. 73, 1673 (1951); its 1-methyl, 3-methyl, and 3-t-butyl derivatives are described in J. Med. Pharm. Chem. 4, 335 (1961), the 2-methyl derivative in French Patent M-2165; the 4-methyl and 3-fluoro derivatives in Belgian Patent 582,220; the 1,4-dimethyl derivative in J. Indian Chem. Soc. 37, 379 (1960); the 2-chloro and 3-chloro derivatives in J. Org. Chem. 27, 230 (1962); the 1-chloro and 3-bromo derivatives in J. Med. Chem. 8, 829 (1965); the 2,7-dibromo derivative in Acta Chem. Scand. 18, 2437 (1963); the 3-trifluoromethyl derivative in Netherlands Patent 67.07356; the 4-amino and 4-methylamino derivatives in U.S. Patent 3,458,578; the 2-hydroxy, 3-hydroxy, 2-methoxy, 3-methoxy, and 2-acetoxy derivatives in U.S. Patent 3,350,405; the 3-methylthio, 3-methylsulfonyl, 3-dimethylaminosulfonyl, and 3-bromo-7-dimethylaminosulfonyl derivatives in Netherlands Patent 65.17266; and the 3,7- and 3,9-dinitro derivatives in Helv. Chim. Acta. 36, 1489 (1953).

A convenient process for preparing the compounds of this invention of formula I comprises the following steps.

A 10,11-dihydrodibenzocyclohepten-5-one of the formula II in which R has the significance defined above is treated with a reducing agent such as an alkali metal borohydride, or hydrogen and a noble metal catalyst, or zinc and sodium hydroxide, preferably sodium borohydride in an alcoholic solvent such as ethanol and at the reflux temperature of the mixture to obtain the corresponding 5-hydroxy derivative of formula III, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol. Said last-named compound is treated at a temperature between 0° and 25° with a halogenating agent such as a hydrohalic acid, preferably anhydrous hydrochloric acid in an inert hydrocarbon solvent, preferably toluene, to obtain the corresponding 5-halo derivative of formula IV in which X represents a halogen with an atomic weight greater than 19; when using hydrochloric acid the product obtained is 5-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene; treating said 5-halo derivative of formula IV with a heavy metal cyanide, preferably silver cyanide in a hydrocarbon solvent such as for example, toluene, and at a temperature up to the boiling point of the mixture yields the corresponding 5-nitrile derivative of formula V, 5-cyano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene. When using as starting material any of the substituted 5-ketones of formula II described earlier in this Application, the corresponding substituted 5-cyano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene is obtained. These reactions are shown in the following formulae in which R and X are as defined above.




Alternatively, a 10,11-dihydro-dibenzocyclohepten-5-one of formula II in which R has the significance defined above may be treated with a Grignard reagent prepared from magnesium and a lower alkoxymethyl halide or a lower alkyl halide in which the halogen atom has an atomic weight greater than 19, in an inert ether-type solvent.

This reaction is carried out at temperatures between 0°C and the reflux temperature of the mixture, for periods of time of from 2-24 hours. Preferred conditions include the use of diethyl ether or tetrahydrofuran as the solvent, of reaction temperatures between 0°C and room temperature, and of reaction times of from 4-12 hours. Decomposition with ammonium chloride, extraction with a water-immiscible solvent, and evaporation of the latter yields the corresponding 5-hydroxy-5-alkyl or 5-hydroxy-5(lower alkoxy)methyl derivative of formula VI in which A represents a lower alkyl or a lower alkoxy group. For example, when using Grignard reagents prepared from ethyl bromide or from methoxym thyl chloride (commercially available as chloromethyl

methyl ether), the compounds obtained are 5-ethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol or 5-methoxymethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol, respectively. Said last-named compound of formula VI in which A represents a lower alkoxy group is then treated with an acid, preferably formic acid, at an elevated temperature preferably at the reflux temperature of the mixture, for periods of time of from one to several hours. Dilution with water, extraction with a water-immiscible solvent and evaporation of the latter yields the corresponding carbonyl derivative of formula VII in which $R^3$ represents hydrogen, and R is as defined in the first instance, i.e. 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-aldehyde or, when using as starting material any of the substituted 5-ketones described earlier in this Application, the correspondingly substituted 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-aldehyde.

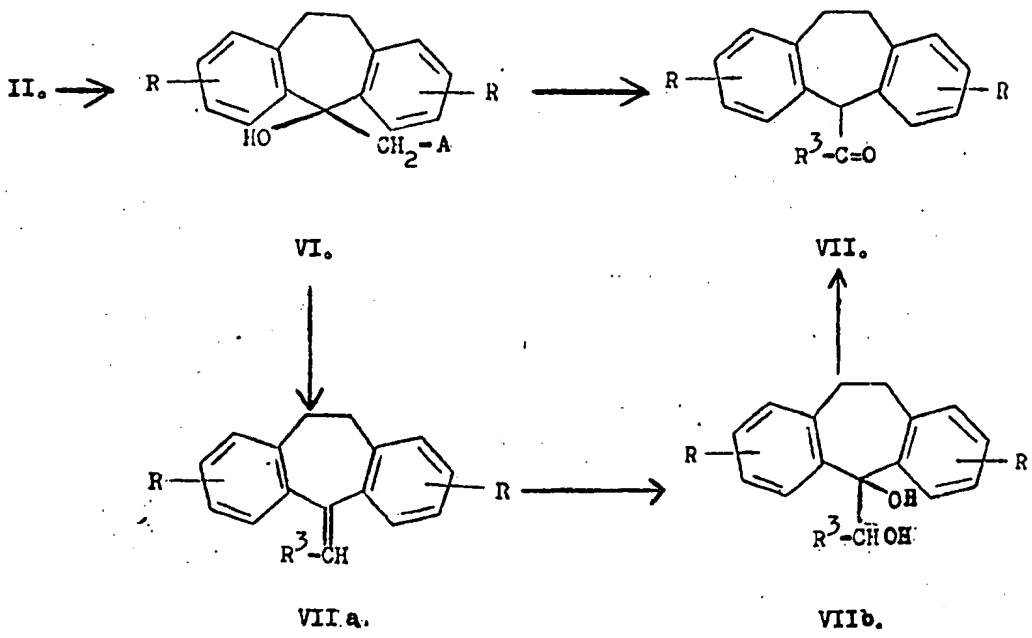
Alternatively, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-aldehyde may also be prepared in the manner described by Ackermann et al., in Can. J. Chem. Vol. 47, 4327 (1969), by treating 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (II) in solution in dimethylsulfoxide and in the presence of sodium hydride with a molar excess of trimethylsulfonium iodide to obtain the corresponding epoxide, spiro-{10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5,2'-epoxide} and treating the latter compound with boron trifluoride etherate, to obtain the desired 5-aldehyde of formula VII in which R and $R^3$ are both hydrogen.

Alternatively, a 5-hydroxy-5-lower alkyl derivative of formula VI in which R is as defined in the first instance and A represents a lower alkyl group, is treated with a

dehydrating agent, preferably, acetic anhydride and/or acetyl chloride for 2-60 minutes at a temperature from 20-100°C, followed by heating under reduced pressure at an elevated temperature, to obtain the corresponding unsaturated derivative of formula VIIa in which R is as defined in the first instance and $R^3$ represents a lower alkyl group. Preferred conditions for this reaction include treatment with a 1:1 mixture of acetic anhydride and acetyl chloride for 5-25 minutes at about 50°C, quenching with ice, extraction with a water-immiscible solvent, evaporation of the latter, and distillation of the residue, to obtain the corresponding unsaturated derivatives of formula VIIa. When using, for example 5-ethyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ol as starting material, the compound thus obtained is 5-ethylidene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene(VIIa,R=H,$R^3$,$CH_3$)

Said last-named compound of formula VIIa is treated with an organic peracid at an elevated temperature for several hours to obtain the corresponding diol of formula VIIb, in which $R^3$ represents a lower alkyl group, which is in turn treated with a mineral acid, preferably dilute sulphuric acid at an elevated temperature for several hours to obtain the corresponding compound of formula VII in which R is as defined in the first instance and $R^3$ is lower alkyl. Preferred conditions for the above reactions include the use of performic acid, prepared in situ from formic acid and hydrogen peroxide, at temperatures of from 50-100°C, for 2-4 hours, dilution with water, extraction with a water-immiscible solvent, evaporation of the latter, heating the residue with 25 per cent (volume by volume) sulfuric acid at the reflux temperature of the mixture for 2-4 hours, extraction with a water-immiscible solvent, evaporation of the latter, and distilling

the residue under reduced pressure, to obtain th corresponding compound of formula VII in which R is as defined in the first instance and $R^3$ is lower alkyl. When using, for example, the 5-ethylidene derivative described above in this sequence of reactions, the compound obtained is 5-acetyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, and when using as initial starting material any of the substituted 5-ketones described earlier in this Application, the correspondingly substituted 10,11-dihydro-5-acetyl-5H-dibenzo[a,d]cycloheptenes are obtained. In the same manner, when using Grignard reagents prepared from propyl, butyl or pentyl halides and proceeding as above, the corresponding 5-propionyl, 5-butanoyl, and 5-pentanoyl derivatives are also obtained. These reactions are shown in the following formulae in which R, $R^3$ and A have the significance defined above.




VII a. VII b.

The carbonyl derivative of formula VII in which $R^3$ represents hydrogen or a lower alkyl group and R is as defined in the first instance is then treated with hydroxylamine to obtain the corresponding oxime of the formula VIII, and said oxime of formula VIII is treated with a reducing agent, preferably Raney nickel alloy or hydrogen in the presence of a heavy metal catalyst, to obtain the corresponding amine of formula IX in which $R^1$ represents hydrogen and R and $R^3$ are as defined in the first instance. Thus, when using as starting material the compound of formula VII in which R and $R^3$ both represent hydrogen, viz., 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-aldehyde, there is obtained the corresponding amine of formula IX, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylmethylamine; and when using as starting material the compound of formula VII in which R is hydrogen and $R^3$ is methyl, viz., 5-acetyl-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene, there is obtained the amine of formula IX in which

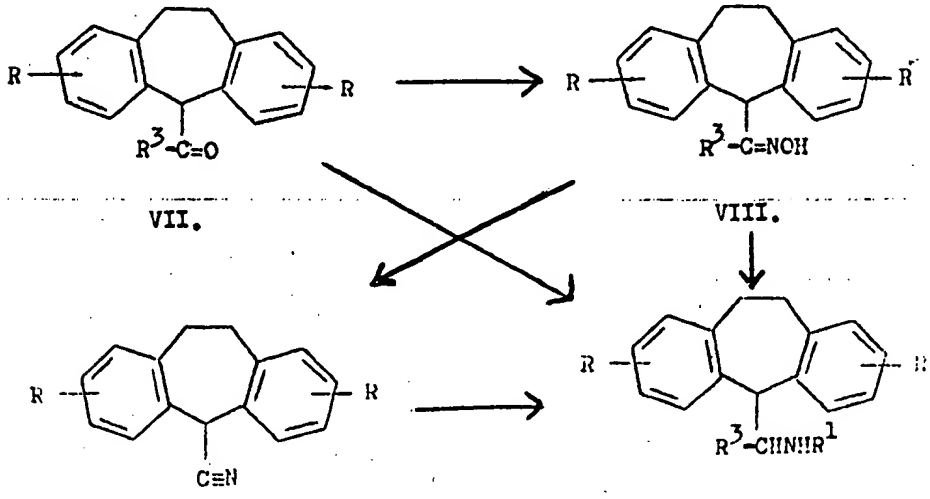
R and $R^1$ are both hydrogen and $R^3$ is methyl, viz. 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine. Similarly, when using any of the substituted derivatives of formula VII described above as starting materials, i.e. any of the compounds of formula VII in which R and $R^3$ are as defined in the first instance except that R may not be hydrogen, the correspondingly substituted amines of formula IX are obtained. These reactions are preferably carried out at about room temperature in an aqueous lower alkanol as the solvent and in the presence of an alkali metal hydroxide.

Alternatively, said oxime of formula VIII in which $R^3$ represents hydrogen and R is as defined in the first instance may be treated with a dehydrating agent, preferably acetic anhydride, at an elevated temperature, preferably at the reflux temperature of the mixture, to obtain the corresponding nitrile of formula V, and said nitrile is treated with a reducing agent, preferably Raney nickel alloy in an alkaline medium or a noble metal catalyst in the presence of hydrogen, preferably at or about room temperature, to obtain the corresponding amine of formula IX in which $R^1$ and $R^3$ represent hydrogen and R is as defined in the first instance.

As another alternative, a carbonyl derivative of formula VII in which R and $R^3$ are as defined in the first instance is treated with an amine of the formula $R^1NH_2$ in which $R^1$ is as defined in the first instance in solution in an inert solvent and in the presence of hydrogen and a catalyst, at a temperature within the range of from 50-150°C, and at a pressure above atmospheric pressure. Preferred conditions include the use of a lower alkanol as the solvent, of Raney nickel as a catalyst, of hydrogen at a pressure of 1000-1500 p.s.i.,

and of a temperature range of from 70-100°C for a period of time of about two hours. The amine of formula IX in which R, $R^1$ and $R^3$ have the significance defined above thus obtained may be isolated by evaporation of the solvent or by precipitation as an insoluble salt, preferably the hydrochloride salt, from which it may be regenerated by addition of alkali. For example, when starting with 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-aldehyde and using ethylamine in the above process, there is obtained N-ethyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (IX, R and $R^3$ = H, $R^1$ = $C_2H_5$), and when starting with 5-acetyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene and again using ethylamine as above, there is obtained N-ethyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (IX, R = H, $R^1$=$C_2H_5$, $R^3$ = $CH_3$). Similarly, when using as starting materials any of the compounds of formula VII in which R and $R^3$ are as defined in the first instance except that R may not be hydrogen, and reacting it with any amine of the formula $R^1 NH_2$ in which $R^1$ is as defined in the first instance, the correspondingly substituted amines of formula IX are obtained.

These reactions are shown in the following formulae in which R, $R^1$ and $R^3$ are as defined in the first instance.



Another alternative for obtaining said amine of formula IX consists in treating a ketone of formula II in which R is as defined in the first instance, with a lower alkyl ester of an α-haloalkanoic acid of formula $XCHR^3COO$(lower alkyl) in which X is a halogen with an atomic weight greater than 19, and $R^3$ is as defined in the first instance, in the presence of zinc metal under the standard conditions of the Reformatskii reaction such as described, for example, in "Organic Reactions", Vol. 1, John Wiley & Sons, New York 1942, or with a lower alkyl ester of an alkanoic acid of the formula $R^3CH_2COO$(lower alkyl) in which $R^3$ is as defined in the first instance, in the presence of a Grignard reagent prepared from a lower alkyl halide and a di-(lower alkyl)amine in an inert solvent under the conditions of a the reaction described by Sisido et al. in J. Am. Chem. Soc., Vol. 74, p. 6254 (1952). Preferred conditions include the use of diethyl ether as a solvent, of ethyl bromide as the lower alkyl halide, of diethylamine as the di-(lower alkyl)amine, and of the methyl, isopropyl or t-butyl esters of the α-haloalkanoic acid or of the alkanoic acid. In both cases there is obtained the corresponding 5-hydroxy-5-alkanoic acid lower alkyl ester of formula X in which R and $R^3$ are as defined in the first instance. In this manner, when starting with the 5-ketone of formula II in which R is hydrogen and reacting it with, for example methyl,isopropyl, or t-butyl bromoacetate or methyl,isopropyl, or t-butyl propionate, there are obtained (5-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl) acetic acid methyl,isopropyl, or t-butyl ester (X, R = $R^3$ = H, lower alkyl = methyl,isopropyl, or t-butyl) and 2-(5-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cycloh pten-5-yl)propi nic acid methyl,

isopropyl, or t-butyl ester (X, R = H, $R^3$ = $CH_3$ , 1 wer alkyl = methyl,isopropyl or t-butyl). When starting with a 5-ketone of formula II in which R has the significance defined in the first instance except that it may not be hydrogen and proceeding as above, there are obtained the correspondingly substituted derivatives of the compounds of formula X named above.

Said compound of formula X is then treated with a mineral acid in a solvent under anhydrous conditions at a temperature within the range of from 0°C to room temperature, to yield the corresponding 5-ylidenealkanoic acid of formula XI in which R and $R^3$ are as defined in the first instance. Preferred conditions for this combined hydrolysis and dehydration include the use of a mixture of chloroform and glacial acetic acid as solvent, of anhydrous hydrogen bromide as the mineral acid,and of a reaction temperature within the range of from 10°C-15°C. Alternatively, said last-named compound of formula XI in which R is as defined in the first instance and $R^3$ is hydrogen may also be obtained by treating a ketone of formula II with a di-(lower alkyl)malonate in an inert solvent and in the presence of a strongly basic condensing agent, to obtain the corresponding compound of formula XII in which R is as defined in the first instance, and

treating said compound of formula XII at an elevated temperature with a base, to obtain the corresponding 5-ylidenealkanoic acid of formula XI in which R is as defined in the first instance and $R^3$ is hydrogen. Preferred conditions for this reaction include the use of an ether-type inert sonvent, such as, for example tetrahydrofuran or dimethoxyethane, of an alkali metal alkoxide or hydride as the

c ndensing agent, and of aqueous alkali metal hydroxide solution as the base, at temperatures between 50-150°C, for periods of time of from 2-24 hours.

As another alternative for obtaining said compound of formula XI in which R and $R^3$ are as defined in the first instance, a ketone of formula II is treated in an inert solvent in the presence of a base at a temperature between 20°C and the boiling point of the mixture for periods of time of from 1 - 8 hours with a di-(lower alkyl)phosphonoalkanoic acid lower alkyl ester or a di-(lower alkyl)phosphonoalkanoic acid nitrile of the formula (lower alkyl-O)$_2$ P(→O)CH$R^3$M in which $R^3$ is as defined in the first instance and M represents the group COO(lower alkyl) or CN, to obtain the corresponding ylidenealkanoic acid lower alkyl ester or ylidenealkanoic acid nitrile of formula XIII in which R, $R^3$ and M have the significance defined above. Said last-named compound of formula XIII is then treated with a mineral acid or with an alkali metal hydroxide to yield the corresponding 5-ylidenealkanoic acid of formula XI in which R and $R^3$ are as defined in the first instance. Preferred conditions for this reaction include the use of commercially available trimethylphosphonoacetate, of dimethylformamide as the inert solvent, of sodium hydride as the base, of a reaction temperature at or near the boiling point of the mixture and of a reaction time of about 2-4 hours, quenching with water, extraction with a water-immiscible solvent, evaporation of the latter, and treatment of the residue with alkali, preferably in aqueous alcoholic solution, to obtain the 5-ylidenealkanoic acid of formula XI in which R and $R^3$ are as defin d in th first instance.

In this manner, when using as starting materials the compounds of formula X, for example (5-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid methyl ester or 2-(5-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid methyl ester or, more conveniently, the corresponding isopropyl or t-butyl esters, and treating said compounds with hydrogen bromide, or by treating the ketone of formula II in which R is hydrogen with methyl dimethylphosphonoacetate or methyl 2-(dimethylphosphono)-propionate or dimethylphosphonoacetonitrile or 2-(dimethylphosphono)-propionitrile, and treating the resulting ylidene acetic or ylidene propionic acid esters of formula XIII viz., (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)acetic acid or 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propionic acid methyl, isopropyl or t-butyl esters with a mineral acid such as, for example, sulfuric acid, or with an alkali metal hydroxide, for example sodium hydroxide, or the corresponding nitriles of formula XIII, viz., (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)acetonitrile or 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionitrile with an alkali metal hydroxide such as, for example, potassium hydroxide, there are obtained (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene)-acetic acid (XI, R = $R^3$ = H) and 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionic acid (XI, R = H, $R^3$ = $CH_3$), respectively. The former compound (XI, R = $R^3$ = H) is also obtained when treating the 5-ketone of formula II in which R is hydrogen with diethyl malonate, treating the resulting compound of formula XII with potassium hydroxide, to obtain the corresponding free acid and heating said acid to a temperature of from 100 to 200°C.

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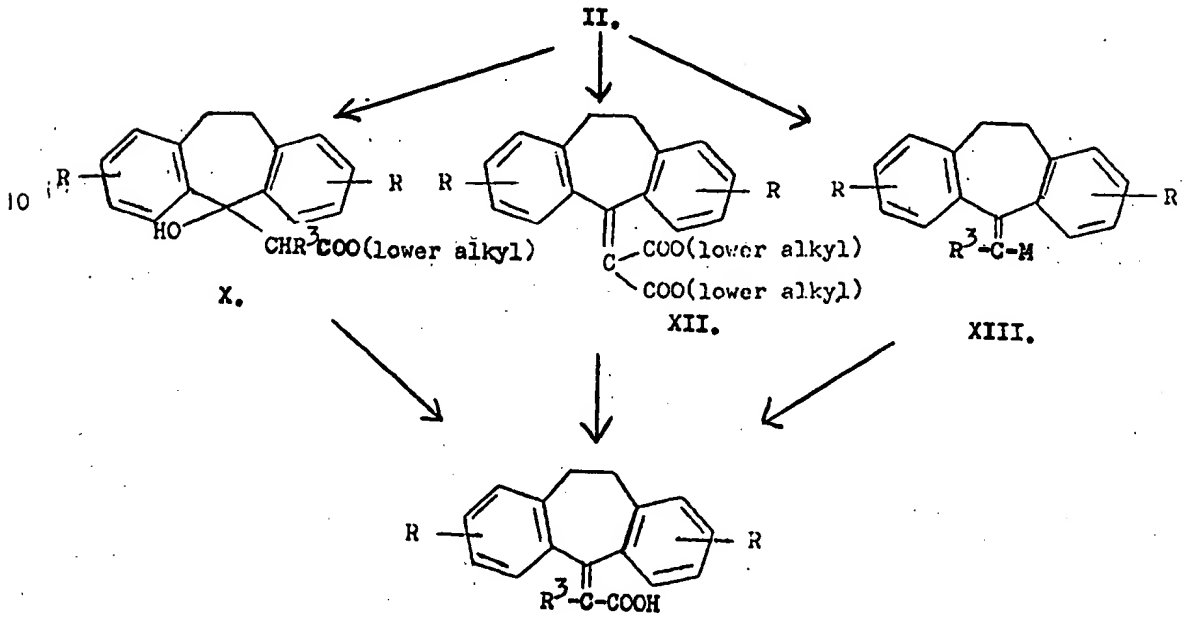
When using as starting materials the appropriately substituted derivatives of the compounds of formulae X or II, i.e. those compounds of formulae X or II in which R is as defined in the first instance except that it may not be hydrogen, the correspondingly substituted derivatives of the ylideneacetic or ylidenepropionic acids of formula XI are obtained.




In the further process for obtaining said amine of formula IX we have found it advantageous to proceed via the corresponding acid amide. Thus, a nitrile of the formula XIII in which R and $R^3$ are as defined in the first instance and M represents the group CN is treated with a hydrating agent to obtain the corresponding ylidenealkanoic acid amide of formula XIV. Preferred conditions for this reaction include the use of sulfuric acid or an alkali metal hydroxide, preferably potassium hydroxide, as a hydrating agent, reaction temperatures within the range of from 50-150°C, and reaction times of from 1-48 hours.

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Extraction with a water-immiscible solvent and evap ration of the latter yields the corresponding ylidenealkanoic acid amide of formula XIV in which R and $R^3$ are as defined in the first instance.

In this manner, when using as starting material for example (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene)-acetonitrile (XIII, R = $R^3$ = H, M = CN) or 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionitrile (XIII, R = H, $R^3$ = $CH_3$, M = CN) and treating with sulfuric acid or preferably potassium hydroxide, there are obtained the corresponding (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetamide (XIV, R = $R^3$ = H) and 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionamide (XIV, R = H, $R^3$ = $CH_3$), respectively.

Alternatively, the same compound of formula XIV is also obtained by treating a ketone of the formula II with a di-(lower alkyl)phosphonoalkanoic acid amide of the formula (lower alkyl-O)$_2$P(→O)$CHR^3CONH_2$ in which $R^3$ is as defined in the first instance, in an inert solvent in the presence of a base. Preferred conditions for this reaction include the use of diethylphosphonoacetic acid amide or 2-(diethylphosphono)-propionic acid amide, of sodium hydride in dimethylformamide as the base, reaction temperatures of from room temperature to the boiling point of the mixture and of reaction times of from 1-8 hours, preferably 2-4 hours, quenching with water, extraction with a water-immiscible solvent and evaporation of the latter.

When using as starting materials the substituted compounds of formulae XIII or II in which R is as defined in the first instance

exc pt that it may n t be hydrogen, th correspondingly substituted ylidene alkanoic acid amides of formula XIV are obtained.

The ylidenealkanoic acid amide of formula XIV in which R and $R^3$ are as defined in the first instance obtained in this manner is then treated with hydrogen in the presence of a noble metal catalyst, preferably 10% palladium on charcoal in suspension in an anhydrous lower alkanol, preferably ethanol, to yield the corresponding 5-alkanoic acid amide of formula XVI in which R and $R^3$ are as defined in the first instance. When using as starting materials any of the ylidene-alkanoic acid amides of formula XIV described in the preceding paragraph there are obtained, for example, (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide (XVI, R = $R^3$ = H), 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionamide (XVI, R = H, $R^3$ = $CH_3$) and their substituted derivatives of formula XVI in which R is other than hydrogen as defined in the first instance.

As another alternative, an ylidenealkanoic acid of formula XI may be treated with a reducing agent such as, for example, hydrogen and a noble metal catalyst, in solution in an anhydrous alkanol, to obtain the corresponding 5-alkanoic acid of formula XV in which R and $R^3$ are as defined in the first instance. Preferred reaction conditions include the use of palladium on charcoal as catalyst and of anhydrous ethanol as the solvent. In this manner, when starting with a compound of formula XI in which R is hydrogen (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid or 2-(10,11-dihydro-5H-dibenzo[a,d]cyclo-h pt n-5-ylid n )-pr pionic acid or th ir substitut d derivatives

in which R has the significance other than hydrog n defined in the first instance there are obtained the corresponding 5-alkanoic acids (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid (XV, R = $R^3$ = H), 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid (XV, R = H, $R^3$ = $CH_3$), and their substituted derivatives in which R has the significance other than hydrogen defined in the first instance, respectively.

The 5-alkanoic acid of formula XV obtained as described above is then treated with a halogenating agent to obtain the corresponding acid halide, and the latter compound is treated in solutionin a solvent with ammonia to obtain the corresponding 5-alkanoic acid amide of formula XVI. Preferred conditions for these steps include the use of thionyl chloride as halogenating agent and of concentrated aqueous ammonia in acetone as the solvent.

In another alternative for obtaining the above amide of formula XVI an ylidenealkanoic acid of formula XI is treated with a halogenating agent to obtain the corresponding ylidenealkanoic acid halide, treating the latter in a solvent with ammonia to obtain the corresponding ylidenealkanoic acid amide of formula XIV, and treating said last-named compound with a reducing agent such as, for example, hydrogen and a noble metal catalyst, to obtain the corresponding alkanoic acid amide of formula XVI. Preferred reaction conditions include the use of thionyl chloride as the halogenating agent, of concentrated aqueous ammonia in acetone, and of hydrogen with palladium on charcoal as the noble metal catalyst as the reducing agent.

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As still another alternative, an ylidenealkanoic acid lower alkyl ester of formula XIII in which M represents the group COO(lower alkyl) and R and $R^3$ are as defined in the first instance is treated in a solution in a solvent with ammonia to yield the corresponding ylidenealkanoic acid amide of formula XIV, and said last-named compound is treated with a reducing agent, for example hydrogen and a noble metal catalyst, to yield the corresponding 5-alkanoic acid amide of formula XVI. Preferred conditions for these steps include the use of a lower alkanol as the solvent and of hydrogen as the reducing agent with palladium on charcoal as the noble metal catalyst.

In this reaction, the order of steps may also be reversed, as follows. An ylidenealkanoic acid lower alkyl ester of formula XIII in which M represents the group COO(lower alkyl), and R and $R^3$ are as defined in the first instance, for example (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid methyl ester, 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionic acid methyl ester, or their substituted derivatives in which R has the significance other than hydrogen defined in the first instance, is treated with a reducing agent, for example hydrogen and a noble metal catalyst, to yield the corresponding alkanoic acid lower alkyl ester of formula XVII in which R and $R^3$ are as defined in the first instance, in this case (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid methyl ester (XVII, $R = R^3 = H$, lower alkyl = $CH_3$), 2-(10,11-dihydr -5H-dib nzo[a,d]-cyclohepten-5-yl)-propionic acid m thyl est r (XVII, R = H, $R^3 = CH_3$, l w r alkyl = $CH_3$) and th ir

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substituted derivatives of formula XVII in which R has the significance other than hydrogen defined in the first instance. Said last-named compound is then treated with ammonia in solution in a solvent to obtain the corresponding alkanoic acid amide of formula XVI. Preferred conditions for these steps are the same as listed immediately above.

As another alternative, an alkanoic acid lower alkyl ester of formula XVII is treated with a mineral acid or with an alkaki metal hydroxide to obtain the corresponding alkanoic acid of formula XV which is then converted to its corresponding alkanoic acid amide of formula XVI in the manner described above.

In these various manners, when starting with any of the ylidenealkanoic acids or their lower alkyl esters of formulae XI or XIII, or with any of the 5-alkanoic acids or their lower alkyl esters of formulae XV and XVII, and proceeding as described above, there are obtained the corresponding amides of formula XVI, viz., (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide (XVI, R = $R^3$ = H), 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionamide (XVI, R = H, $R^3$ = $CH_3$), and their substituted derivatives of formula XVI in which R has the significance other than hydrogen defined in the first instance, respectively.

In still another alternative pathway for preparing the alkanoic acid amide of formula XVI, a 5-hydroxy derivative of formula III in which R is as defined in the first instance is treated with an α-cyanoalkanoic acid of the formula $R^3CH(CN)COOH$

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or with an α-cyanoalkanoic acid low r alkyl ester of the formula $R^3CH(CN)COO$(lower alkyl) in which $R^3$ is as defined in the first instance in an acid solvent and in the presence of an acidic catalyst, to yield the corresponding nitrile of formula XVIII in which R and $R^3$ are as defined in the first instance, and the latter compound is either treated with a hydrating agent, such as sulfuric acid, a mixture of sulfuric and acetic acids, or a dilute solution of an alkali metal hydroxide in a lower alkanol, to obtain the corresponding alkanoic acid amide of formula XVI, or with a mineral acid or an alkali metal hydroxide to obtain the corresponding alkanoic acid of formula XV from which the corresponding alkanoic acid amide XVI is prepared as described above.

Preferred conditions for the condensation of the 5-hydroxy derivative of formula III with the α-cyanoalkanoic acid of the formula $R^3CH(CN)COOH$ or its corresponding lower alkyl ester are similar to those described by Goldberg and Wragg in J. Chem. Soc. 1957, p. 4823. The preferred solvent is glacial acetic acid and the preferred acidic catalyst is anhydrous zinc chloride. The reaction is carried out at an elevated temperature, preferably at the reflux temperature of the mixture, for periods of tome of from 4-24 hours, preferably 6-12 hours. Dilution with water, extraction with a water-immiscible solvent and evaporation of the latter yields the corresponding nitrile of formula XVIII in which R and $R^3$ are as defined in the first instance.

Alternatively, the nitrile of formula XVIII is also obtained by treating a compound of the formula XIII in which $R^3$ is as defined in the first instance and M represents the group CN with hydrog n in the pres nce of a m tal catalyst. Pref rred c nditions

for this reaction include the use of palladium on charcoal as catalyst and of ethanol as the solvent.

The preferred hydrating agents for converting the above nitrile of formula XVIII to the corresponding amide of formula XVI are 57% aqueous sulfuric acid, or a mixture of sulfuric acid, glacial acetic acid and water (1:1:1 by volume) or 3-8% potassium hydroxide in solution in a lower alkanol, preferably isopropanol. Treatment of the nitrile of formula XVIII with the above reagents at an elevated temperature, preferably at the reflux temperature of the mixture, for periods of time of from 2-48 hours, preferably 4-24 hours, yields the corresponding amide of formula XVI in which R and $R^3$ are as defined in the first instance.

The preferred agent for converting the nitrile of formula XVIII to the corresponding alkanoic acid of the formula XV is concentrated potassium hydroxide, preferably 20-40%, in solution in an aqueous lower alkanol, preferably ethanol or isopropanol. Refluxing for 8-24 hours, evaporation of the solvent, acidification of the residue, extraction with a water-immiscible solvent, and evaporation of the latter yields the corresponding alkanoic acid of the formula XV in which R and $R^3$ are as defined in the first instance.

In the manner described above, when starting with 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol (III, R = H) or with any of its substituted derivatives of formula III in which R has the significance other than hydrogen defined in the first instance, and reacting said compound of formula III with cyanoac tic acid or α-cyanopropionic acid, r with th ir respective

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lower alkyl, e.g. ethyl esters, there are obtained the corresponding nitriles of formula XVIII, viz., (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetonitrile (XVIII, R = $R^3$ = H), 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionitrile (XVIII, R = H, $R^3$ = $CH_3$), and their substituted derivatives of formula XVIII in which R has the significance other than hydrogen defined in the first instance. Said compounds are then converted in the various manners described above either to the corresponding alkanoic acids of formula XV or to the corresponding amides of formula XVI, both described above.

Alternatively, a 5-ketone of formula II is treated with acetylene in the presence of a basic condensing agent such as, for example, sodium amide, to obtain the corresponding 5-hydroxy-5-ethynyl derivative of formula XIX; the latter compound is treated with an acid isomerizing agent such as, for example, sulfuric acid to obtain the corresponding aldehyde of formula XX, which is in turn treated with an oxidizing agent such as, for example, silver nitrate, to obtain the corresponding ylidene-alkanoic acid of formula XI in which $R^3$ represents hydrogen, from which the corresponding alkanoic acid of formula XV and finally the corresponding alkanoic acid amide of formula XVI is prepared as described above.

Preferred conditions for these reaction steps are similar to those described, for example, in the chapter "Acetylene Chemistry" on pp. 134 ff. of "Progress in Organic Chemistry", Vol. 1, Butterworths, London 1952. They include

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th use of s dium amide prepared in situ from sodium and liquid ammonia as the basic condensing agent, mixtures of liquid ammonia and diethyl ether as solvent, reaction temperatures of from -60°C to room temperature, and reaction times of from 6-24 hours. In this manner, when starting with 10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-one (II,R = H) or with any of its substituted derivatives of formula II in which R has the significance other than hydrogen defined in the first instance, there is obtained 10,11-dihydro-5-ethynyl-5H-dibenzo[a,d]cyclohepten-5-ol (XIX,R = H) or its substituted derivatives of formula XIX in which R has the significance other than hydrogen defined in the first instance, respectively. Preferred conditions also include the use of approximately 30% aqueous sulfuric acid as the isomerizing agent, and carrying out the isomerisation in solution in a lower alkanol, for example ethanol, at an elevated temperature, preferably at the reflux temperature of the mixture, for periods of time of from 5-60 minutes. Cooling, followed by filtration yields (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetaldehyde (XX, R = H) or its substituted derivatives of formula XX in which R has the significance other than hydrogen defined in the first instance, respectively. Preferred conditions for the subsequent oxidation reaction include the use of an aqueous solution of silver nitrate mixed with a solution of the appropriate aldehyde of formula XX in a lower alkanol, preferably ethanol, and introducing said mixture into an aqueous alkanolic solution of potassium hydroxide. Filtration, washing, acidification of the filtrates and washings with dilute nitric acid, filtration and crystallization yields the c rr sp nding ylid ne-

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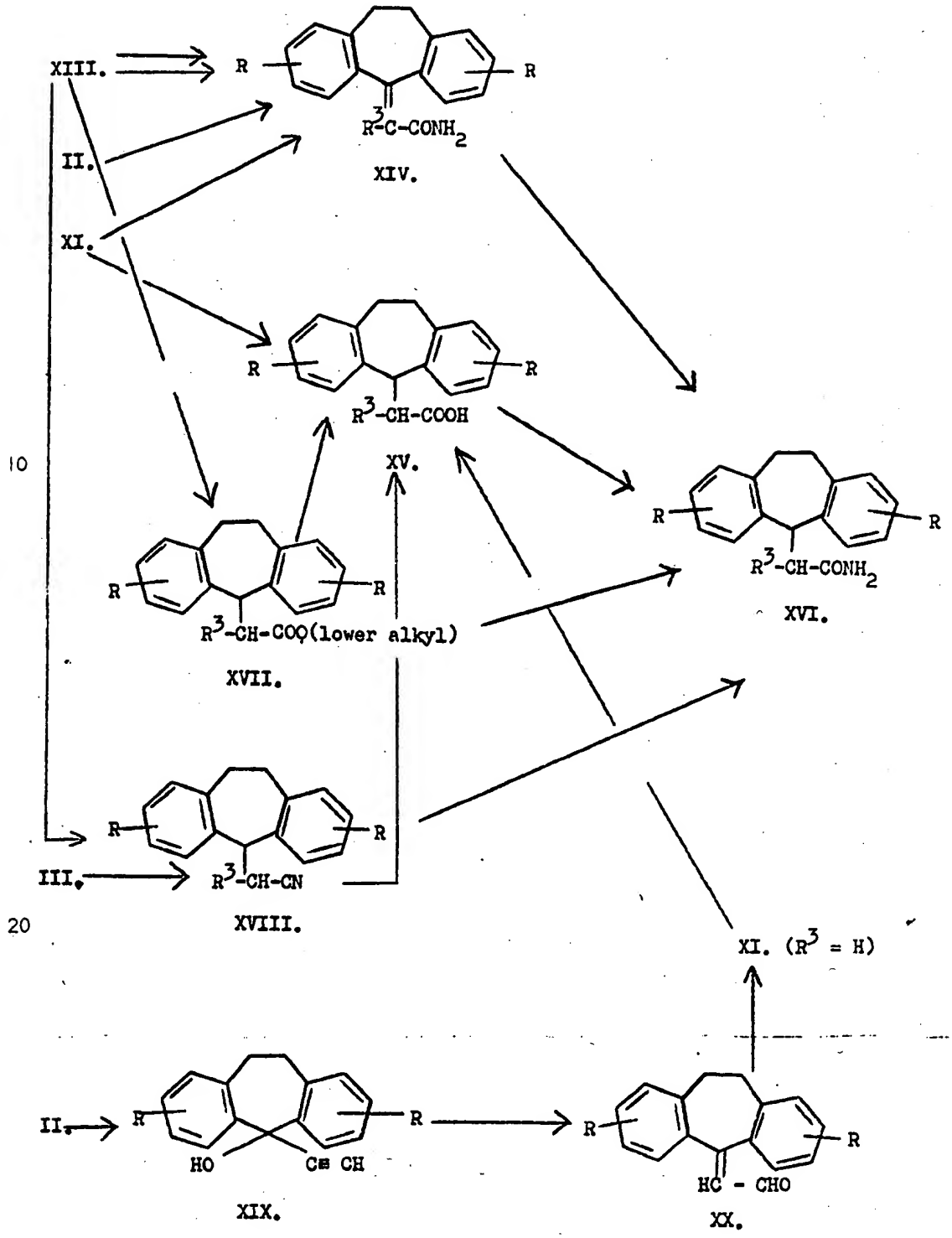
ac tic acid of f rmula XI ($R^3$ = H) described earli r in this Application, from which the corresponding 5-alkanoic acid of formula XV ($R^3$ = H) described earlier in this Application is obtained by treatment with a reducing agent, preferably palladium on charcoal and hydrogen, as described above. The corresponding amide of formula XVI ($R^3$ = H), also described earlier in this Application, is then obtained from said 5-alkanoic acid in the manner described above.

These reactions are shown in the following formulae in which R and $R^3$ have the significance defined above.


XIII.
II.
XI.
R
R
$R^3$-C-CONH$_2$
XIV.
$R^3$-CH-COOH
XV.
$R^3$-CH-CONH$_2$
XVI.
$R^3$-CH-COO(lower alkyl)
XVII.
III.
$R^3$-CH-CN
XVIII.
XI. ($R^3$ = H)
II.
HO
C≡ CH
XIX.
HC - CHO
XX.

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Additional pathways for preparing the alkanoic acid amide of formula XVI include the reaction of a 5-halo derivative of formula IV in which R and X are as defined in the first instance with an alkali metal or an alkali earth metal derivative of a di-(lower alkyl) malonate of the formula $(Met)R^3C(COOQ)_2$ in which Met represents an alkali or an earth alkali metal, $R^3$ is as defined in the first instance, and Q represents a lower alkyl group, to obtain the corresponding compound of formula XXI in which R, $R^3$ and Q are as defined above. Said last-named compound of formula XXI in which R, $R^3$ and Q are as derined above is treated at an elevated temperature with a base to yield the corresponding compound of formula XXI in which R and $R^3$ are as defined above and Q is hydrogen. Heating said last-named compound at an elevated temperature yields the corresponding alkanoic acid of formula XV in which R and $R^3$ are as defined in the first instance, from which the corresponding alkanoic acid amide of formula XVI in which R and $R^3$ are as defined above is prepared as described above. Preferred conditions for this reaction include the use of sodium as the alkali metal or of magnesium as the alkali earth metal, of diethylmalonate or of a lower alkyl derivative thereof, and carrying out the condensation reaction in solution in a solvent such as a lower alkanol or an ether or cyclic ether; preferably, the metal salt of the dialkylmalonate is formed in ethanol which is then removed and replaced by tetrahydrofuran for the condensation. In the transformation of the resulting compound of formula XXI to the corresponding free acid

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of formula XXI in which Q is hydrogen it is advantageous to use as a base an alkali metal hydroxide, preferably potassium hydroxide in aqueous ethanol at the reflux temperature of the mixture. The resulting free acid of formula XXI in which Q is hydrogen and R and $R^3$ are as defined above is then heated at a temperature within the range of from 100-200°C, preferably at 150-180°C, to yield the corresponding alkanoic acid of formula XV, from which the corresponding amide of formula XVI is obtained as described earlier in this Application.

In this manner, when starting with 5-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (IV, R = H) or with any of its substituted derivatives of formula IV in which R has the significance other than hydrogen as defined in the first instance, and condensing it in the manner described above with diethyl malonate or with diethyl 2-methylmalonate, there is first obtained the corresponding compound of formula XXI in which Q is lower alkyl, viz., 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-malonic acid diethyl ester (XXI, R = $R^3$ = H, Q = $C_2H_5$), 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methylmalonic acid diethyl ester (XXI, R = H, $R^3$ = $CH_3$, Q = $C_2H_5$), or their substituted derivatives of formula XXI in which R has the significance other than hydrogen defined in the first instance. Treating any of said compounds of formula XXI at an elevated temperature with a base yields the corresponding free acids of formula XXI, viz., 2-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-malonic acid (XXI, R = $R^3$ = Q = H), 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methylmalonic acid (XXI, R = Q = H, $R^3$ = $CH_3$), and th ir corresponding derivatives

f formula XXI in which $R^3$ is as defined in the first instance, Q is hydrogen, and R has the significance other than hydrogen defined in the first instance. Heating any of said last-named compounds at 100-200°C yields the corresponding alkanoic acid of formula XV from with the corresponding amide of formula XVI is obtained as described earlier in this Application. Both these compounds of formula XV and of formula XVI have also been described above.

Alternatively, a compound of formula XII is treated with hydrogen and a noble metal catalyst to obtain the corresponding compound of formula XXI in which Q represents a lower alkyl group and in which $R^3$ represents hydrogen. Treatment of said last-named compound with a base in the manner described above yields the corresponding free acid of formula XXI in which $R^3$ and Q both represent hydrogen. Heating said last-named compound to 100-200°C in the manner described above yields the corresponding alkanoic acid of formula XV in which $R^3$ represents hydrogen, and said last-named compound is converted to the corresponding alkanoic acid amide of formula XVI in which $R^3$ represents hydrogen in the manner described above. Preferred conditions include the use of palladium on charcoal as the catalyst and of aqueous ethanolic potassium hydroxide as the base.

Alternatively said compound of formula XXI in which R and $R^3$ are as defined in the first instance and Q represents hydrogen is obtained by treating a 5-hydroxy derivative of formula III with a malonic acid of the formula $R^3CH(COOH)_2$ in which $R^3$ is as defined in the first instance, at an elevated temperature and

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in a solvent. Treatment of said compound of formula XXI in which R, $R^3$ and Q are as defined above with an organic base at an elevated temperature followed by acidification yields the corresponding alkanoic acid of formula XV in which R and $R^3$ are as defined in the first instance, and the conversion of the latter compound to the corresponding amide of formula XVI is carried out as described above. The conversion of said last-named compound of formula XXI to the corresponding alkanoic acid of formula XV and ultimately to the corresponding alkanoic amide of formula XVI, R and $R^3$ in both formulae being as defined in the first instance may also be carried out in the same manner as described earlier in this Application.

Preferred reaction conditions include the use of glacial acetic acid as solvent and of temperatures between 50°C and 100°C, preferably about 70°C, for periods of time of from 1-5 hours, preferably about 2 hours, followed by standing for 12-24 hours at or about room temperature, to obtain the malonic acid derivatives of formula XXI described above in which R, $R^3$ and Q are as defined above. The preferred organic base for the subsequent decarboxylation reaction is pyridine at a temperature of from 70-110°C, preferably at about 100°C, to obtain the corresponding alkanoic acid of formula XV described above in which R and $R^3$ are as defined in the first instance.

In another alternative for preparing an alkanoic acid amide of formula XVI a 5-halo derivative of formula IV is treated at an elevated temperature with a Group I metal derivative of a lower alkyl acetoacetate of the formula $CH_3COC(Met)R^3COO$(lower alkyl) in which Met repr sents a

metal and $R^3$ is as defined in the first instance, to obtain the corresponding compound of formula XXII in which $R^3$ is as defined above, and treating said compound of formula XXII with a strong base to obtain the corresponding alkanoic acid of formula XV, from which the corresponding alkanoic acid amide of formula XVI is prepared as described above. Preferred conditions for this reaction include the use of copper as the metal, of carrying out the reaction in a solvent such as an aromatic hydrocarbon, preferably benzene, at a temperature within the range of 50-150°C, preferably at the reflux temperature of the mixture, and of using as the strong base an alkali metal hydroxide, preferably sodium hydroxide.

Thus, when reacting 5-chloro-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene (IV, R = H, X = Cl) with the copper derivative of ethyl acetoacetate in the manner described in U.S. Patent 3,324,138, there is obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetoacetic acid ethyl ester (XXII, R = $R^3$ = H, lower alkyl = $C_2H_5$); when reacting the same compound of formula IV with the copper derivative of ethyl 2-methylacetoacetate, there is obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methylaceto-acetic acid ethyl ester (XXII, R = H, $R^3$ = $CH_3$, lower alkyl = $C_2H_5$); and when using any of the compounds of formula IV in which R is other than hydrogen as defined in the first instance, the correspondingly substituted compounds of formula XXII in which R has the significance other than hydrogen defined in the first instance are obtained.

The above compounds of formula XXII, when heated with

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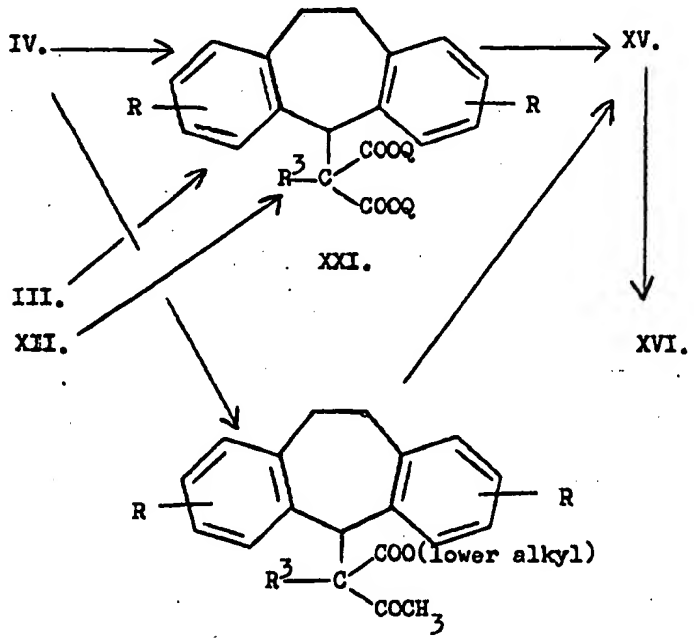
concentrated sodium hydroxide, preferably 50% sodium hydroxide, yield the corresponding alkanoic acids of formula XV described above, from which the corresponding alkanoic acid amides of formula XVI, also described above, are prepared as described earlier in this Application.

These reactions are shown in the formulae in which R, $R^3$ and Q are as defined above.




XXII.

Certain pathways for obtaining the amine of formula IX have been described above. However, it is generally more convenient to prepare said amine either from the corresponding alkanoic acid of the formula XV in which R and $R^3$ are as defined in the first instance, or from the alkanoic acid amide of the formula XVI in which R and $R^3$ are as defined in the first instance. When it is desired to obtain an amine of formula IX

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in which R is a substituent ther than hydrogen, in particular a halogen, for example the 3-chloro substituent, it is particularly advantageous to use the correspondingly substituted (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-carboxamide described by M.A. Davis et al. in J. Med. Chem. 7, 88(1964) as starting material.

An alkanoic acid of formula XV in which R and $R^3$ are as defined in the first instance is converted to the corresponding acid halide by treatment with a halogenating agent, preferably thionyl chloride. The resulting acid halide is treated with an alkali metal azide, preferably sodium azide, to obtain the corresponding acid azide, which is heated to yield the corresponding isocyanate of formula XXIV, Treatment of said last-named isocyanate with a mineral acid yields the corresponding amine of the formula IX in which $R^1$ represents hydrogen and R and $R^3$ are as defined in the first instance. Preferred reaction conditions include the use of a molar excess of thionyl chloride to obtain the corresponding alkanoic acid chloride, removal of excess thionyl chloride, and utilization of the crude acid chloride without further purification. The reaction between the respective acid chloride and sodium azide is carried out in acetone as solvent, preferably at temperatures within the range of from -20°C to 20°C. The conversion of the respective acid azides thus obtained to the corresponding isocyanates of formula XXIV is advantageously carried out by heating in an aromatic hydrocarbon solvent, preferably toluene, and in this manner it is not essential to isolate the resulting isocyanates of formula XXIV. Addition of a strong acid, preferably hydrochloric acid, to th solution of the isocyanat obtained as described

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above, and heating to a temperature within the range of from 50-120°C, preferably to about 80°C, yields the corresponding acid addition salt of the corresponding amine of formula IX, from which the corresponding amine of formula IX in which $R^1$ is hydrogen and R and $R^3$ are as defined in the first instance is obtained by treatment with alkali.

In this manner, when starting with (10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)-acetic acid (XV, R = $R^3$ = H) or with 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid (XV, R = H, $R^3$ = $CH_3$) there are obtained the acid azides (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid azide and 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid azide, respectively; the isocyanates (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylisocyanate (XXIV, R = $R^3$ = H) and 1-(10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)-ethylisocyanate (XXIV, R = H, $R^3$ = $CH_3$), respectively, and the amines (10,11-dihydro-5H-dibenzo[a,d]cyclo-hepten-5-yl)-methylamine (IX, R = $R^1$ = $R^3$ = H) and 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (IX, R = $R^1$ = H, $R^3$ = $CH_3$), respectively. When starting with an alkanoic acid of formula XV in which $R^3$ is as defined in the first instance and R is other than hydrogen as defined in the first instance, and proceeding as above, the correspondingly substituted acid azides, isocyanates of formula XXIV, and amines of formula IX are obtained, R in each case having the significance other than hydrogen defined in the first instance and $R^3$ being as defined in the first instance, with $R^1$ in the amines of formula IX being hydrogen.

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In an advantageous variant of the above procedure th hazards of having to use sodium azide are eliminated in the following manner. An alkanoic acid of formula XV in which R and $R^3$ are as defined in the first instance or its corresponding methyl ester or its corresponding acid halide, preferably the acid chloride, all described above, is treated with hydrazine hydrate to obtain the corresponding acid hydrazide. When it is desired to use the methyl ester of the alkanoic acid XV in the above procedure, said ester is prepared by treating the corresponding acid halide with methanol, or by catalytic reduction of the corresponding ylidene-acetic acid methyl ester of formula XIII. The acid hydrazide is treated with an alkali metal nitrite in solution in a solvent and in the presence of an acid at a temperature between the freezing point of the mixture and +5°C, to yield the corresponding acid azide which is, however, not isolated but is directly converted in the manner described above to an acid addition salt of the corresponding amine of formula IX from which the free amine is obtained by treatment with alkali.

Preferred reaction conditions for this procedure include the following. When using the methyl ester or the acid chloride of the alkanoic acid of formula XV as the starting materials, the reaction with hydrazine hydrate, preferably 99-100% hydrazine hydrate, is carried out in solution in a lower alkanol, preferably isopropanol, and when using the free acid of formula XV the reaction is carried in the absence of a solvent, in all cases at an elevated temperature, preferably at the reflux temperature f the mixtur . C ling f th reaction mixtur , if necessary aft r removal of xc ss solv nt and/ r hydrazine hydrat , yields the corresponding acid hydrazide. Thus, when starting with (10,11-dihydr -5H-dibenzo[a,d]cycloh pten-5-yl)-acetic acid

(XV, R = $R^3$ = H)or with 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid (XV, R = H, $R^3$ = $CH_3$) or with their corresponding m thyl esters or acid chlorides, and proceeding as above, there are obtained (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid hydrazide and 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid hydrazide, respectively. And when starting with any of the alkanoic acids of formula XV in which $R^3$ is as defined in the first instance and R has the significance other than hydrogen defined in the first instance, or with their respective methyl esters or acid chlorides described above, the correspondingly substituted acid hydrazides are obtained.

Preferred conditions for the conversion of said acid hydrazides to the intermediate acid azides include carrying out the reaction with sodium nitrite in solution in a water-immiscible ether-type solvent, preferably tetrahydrofuran, in the presence of a strong mineral acid, preferably hydrochloric acid, and at a temperature preferably not exceeding 0°C, for periods of time of from 30-120 minutes. Addition of cold water and of an aromatic hydrocarbon solvent, preferably toluene, and separation of the organic phase yields a solution of the corresponding acid azide, described above, which is converted in the manner described above to the acid addition salt of the corresponding amine of formula IX in which $R^1$ is hydrogen and R and $R^3$ are as described in the first instance.

Alternatively, an alkanoic acid of the formula XV in which R and $R^3$ are as defined in the first instance is treated with a halogenating agent, preferably thionyl chloride, to yield the corresponding acid halide, which is in turn treated with ammonia to yield the corresponding alkanoic acid amide of the formula XVI in which R and $R^3$ are as d fined in th first instanc . Treatment of said last-nam d acid amide with bromine in solution in

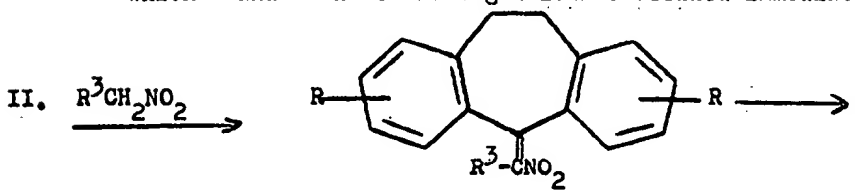
an alkali metal hydroxide, preferably sodium hydroxide, at temperatur s within the range of from room temperature to the reflux temperatur of the mixture, yields the c rre ponding amine of formula IX described earlier in this Application in which $R^1$ represents hydrogen and R and $R^3$ are as defined in the first instance. Preferred reaction conditions include the use of a sodium hypobromite solution previously prepared from sodium hydroxide and bromine, reaction times of from 10 minutes to several hours, preferably about one-half hour, at the reflux temperature of the mixture. The resulting amine is isolated from the reaction mixture by extraction with a water-immiscible solvent, preferably benzene, and is conveniently purified by reacting it with a mineral acid under anhydrous conditions, preferably with hydrogen chloride gas, to form the hydrochloride salt which is easily purified and conveniently transformed to the corresponding amine of formula IX in which R and $R^3$ are as defined in the first instance and $R^1$ is hydrogen.

Alternatively, 3-chloro-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylamine is conveniently prepared from 3-chlorodibenzo[a,d]cycloheptadiene-5-carboxamide, described by M.A. Davis et al. in J. Med. Chem. 7, 88 (1964), by treatment with diborane.

Another alternative for preparing the amine of formula IX in which $R^1$ represents hydrogen and $R^3$ is as defined in the first instance consists in treating a compound of formula II with a nitroalkane of the formula $R^3CH_2NO_2$ in which $R^3$ is as defined in the first instance, in an alkanolic solvent and in the presence of a catalyst, to obtain the corresponding compound of formula XXIII

in which R and $R^3$ are as defined above, and treating said last-named compound with a reducing agent, pr ferably a complex alkali metal aluminum hydride, to obtain the corresponding amine of formula IX in which $R^1$ represents hydrogen and R and $R^3$ are as defined in the first instance. Preferred reaction conditions include the use of ethanol as the solvent and potassium hydroxide as the catalyst, preferably at a temperature, between -20°C and 20°C for periods of time of from 1-6 hours. In this manner, when starting with 10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-one (II, R = H), or with its derivatives of formula II in which R is other than hydrogen as defined in the first instance, and reacting it with nitromethane or nitroethane, there are respectively obtained (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene)-nitromethane, (XXIII, R = $R^3$ = H), 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-nitro-ethane (XXIII, R = H, $R^3$ = $CH_3$), and their derivatives of formula XXIII in which R has the significance other than hydrogen as defined in the first instance.

These reactions are shown in the following formulae in which R and $R^3$ have the significance defined immediately above.




XXIII.

Any of the amines of formula IX obtained in the manner described above in which R and $R^3$ are as defined in the first instance and in which $R^1$ represents hydrogen may be treated with an alkylating agent such as, for example, an alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, or phenylalkyl halide or sulfate, optionally in the presence of a base or of excess amine, t obtain the corresponding amines of formula IX in which $R^1$ represents an alkyl, alkenyl, cycloalkyl, cycloalkylalkyl or phenylalkyl group.

Thus, when reacting (10,11-dihydro-5H-dib nzo[a,d]cyclohepten-5-yl)-methylamine (IX, R = $R^1$ = $R^3$ = H) or 1-(10,11-dihydro-5H-dibenz [a,d]cyclohepten-5-yl)- thylamine (IX, R = $R^1$ = H, $R^3$ = $CH_3$) with, for example, methyl iodide, ethyl iodide, allyl bromide, cyclopentyl bromide, cyclohexylmethyl chloride, or benzyl chloride, there are obtained N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl and N-benzyl (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylamine and N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl and N-benzyl 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine, respectively. When using as starting materials any of the compounds of formula IX in which R is other than hydrogen as defined in the first instance and proceeding as above, the correspondingly substituted derivative of the compounds described immediately above in which R has the significance other than hydrogen as defined in the first instance are respectively obtained.

Alternatively, said last-named amines of formula IX may also be obtained by acylation and subsequent reduction. In this manner, treatment of an amine of formula IX in which R and $R^3$ are as defined in the first instance and $R^1$ is hydrogen with formic acetic anhydride or with an acyl, unsaturated acyl, cycloalkylacyl, or phenyl-acyl halide or anhydride, optionally in the presence of a base preferably pyridine or of excess amine, yields the correspondingly acylated derivatives of the amines of formula IX in which $R^1$ represents the respective acyl group and R and $R^3$ are as defined in the first instance. Treatment of said last-named compounds with a suitable reducing agent, preferably diborane or a complex alkali metal aluminum hydride, yields the amines of formula IX in which R and $R^3$ are as defined in the first instance and $R^1$ represents an alkyl, alkenyl, cycloalkylalkyl, or phenylalkyl group.

Thus, when treating any of the starting materials described in the preceeding paragraph and reacting them in the manner described above with, for example, formic acetic anhydride acetic acid, propenoic acid, cyclohexylcarboxylic acid, or benzoic acid chloride or anhydride, and treating the resulting N-formyl, N-acetyl, N-propenoyl, N-cyclohexylcarbonyl, N-benzoyl derivatives with lithium aluminium hydride, the same N-methyl, N-ethyl, N-allyl, N-cyclohexylmethyl, and N-benzyl derivatives of the amines of formula IX as described immediately above are obtained.

The amine of the formula IX in which R, $R^1$ and $R^3$ are as defined in the first instance is treated with an aldehyde of the formula $R^2CHO$ in which $R^2$ represents hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, phenyl, or phenylalkyl, in the presence of an acid, to obtain the corresponding compound of formula I in which $R^2$ is as defined immediately above, and R, $R^1$ and $R^3$ are as defined in the first instance. The reaction between the amine and the aldehyde is carried out in the presence of a strong acid, preferably a mineral acid such as, for example, hydrochloric acid. Alternatively, the salt of the amine with a strong acid, preferably the hydrochloride salt, may be used as a starting material and may be reacted directly with the aldehyde. The temperature of the reaction may vary from room temperature to the reflux temperature of the mixture and is preferably chosen within the range of from about 80°C to about 100°C. The time of reaction may vary within the range of from one to several hours, depending upon the temperature.

Preferr d reaction conditions include the us of a steam bath and reaction times of about two to five hours. After completion of the reaction, the mixture is cooled, made alkaline, and extracted with a water-immiscible solvent, preferably benzene. After washing and drying of the organic extract the desired compound is obtained by evaporation of the solvent. In this manner, when using as starting materials(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine and 40% aqueous formaldehyde in the presence of aqueous hydrochloric acid, or the hydrochloride salt of the above amine together with 40% aqueous formaldehyde, there is obtained the compound of formula I in which R, $R^1$, $R^2$, and $R^3$ all represent hydrogen, viz., 1,2,3,7,8,12b-hexahydrobenzo [6,7]cyclohepta[1,2,3-d,e]-isoquinoline. When using as starting material the amine of formula IX in which R and $R^1$ both represent hydrogen and $R^3$ represents a lower alkyl group, for example methyl, and reacting said amine with formaldehyde in the presence of hydrochloric acid, or when using the hydrochloride salt of the above amine as the starting material, there are obtained the compounds of formula I in which $R^3$ represents the corresponding lower alkyl group, viz., the corresponding 1-lower alkyl derivatives of formula I, for example 1-methyl-1,2,3,7,8,12β-hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinoline. Alternatively, when using as starting material an amine of formula IX in which R, $R^1$ and $R^3$ represent hydrogen, or its hydrochloride salt, and reacting it in the manner described above, with an aldehyde of

the formula $R^2CHO$ in which $R^2$ represents alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, phenyl, or phenylalkyl, there are obtained the corresponding compounds of formula I in which $R^2$ is as defined immediately above, and R, $R^1$, and $R^3$ represent hydrogen, viz., the 3-alkyl-, 3-alkenyl-, 3-cycloalkyl-, 3-cycloalkylalkyl-, 3-phenyl-, or 3-phenylalkyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolines.

In this manner, when starting with (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine and reacting it with acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, n-pentan-1-al, isopentan-1-al (2-methylbutan-1-al), n-hexan-1-al, isohexan-1-al (4-methylpentan-1-al) n-heptan-1-al, n-octan-1-al, n-nonan-1-al, n-undecan-1-al, vinylacetaldehyde, cyclopropylaldehyde, cyclohexylacetaldehyde, benzaldehyde, or phenylacetaldehyde there are obtained 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexylmethyl-, 3-phenyl-, and 3-benzyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, respectively.

As another alternative, when using as starting material an amine of the formula IX in which R and $R^3$ represent hydrogen and $R^1$ represents alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, or phenylalkyl, or its hydrochloride salt, and reacting it with formaldehyde, in the manner described above, there are obtained the corresponding compounds of formula I in which R, $R^2$ and $R^3$

As still another alternative, when using as starting materials an amine of formula IX in which R and $R^1$ represent hydrogen and $R^3$ is a lower alkyl group, or its hydrochloride salt, and reacting it with an aldehyde of the formula $R^2CHO$ in which $R^2$ is as defined immediately above, in the manner described above, there are obtained the 1,3-dialkyl-, 1-alkyl-3-alkenyl-, 1-alkyl-3-cycloalkyl-, 1-alkyl-3-cycloalkylalkyl-, 1-alkyl-3-phenyl-, and 1-alkyl-3-phenylalkyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinolines. In this manner, when starting with 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine or its hydrochloride salt and reacting it with acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, n-pentan-1-al, isopentan-1-al (2-methylbutan-1-al), n-hexan-1-al, isohexan-1-al (4-methylpentan-1-al) n-heptan-1-al, n-octan-1-al, n-nonan-1-al, n-undecan-1-al, vinylacetaldehyde, cyclopropylaldehyde, cyclohexylacetaldehyde, benzaldehyde, or phenylacetaldehyde there are obtained 1,3-dimethyl-, 1-methyl-3-ethyl, 1-methyl-3-propyl-, 1-methyl-3-isopropyl-, 1-methyl-3-n-butyl-, 1-methyl-3-isobutyl-, 1-methyl-3-n-amyl-, 1-methyl-3-isoamyl-, 1-methyl-3-n-hexyl-, 1-methyl-3-n-heptyl-, 1-methyl-3-n-octyl-, 1-methyl-3-n-decyl-, 1-methyl-3-allyl-, 1-methyl-3-cyclopropyl-, 1-methyl-3-cyclohexylmethyl-, 1-methyl-3-phenyl-, and 1-methyl-3-benzyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, respectively.

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r present hydrogen and $R^1$ is as defined immediately abov , viz., the corresponding 2-alkyl-, 2-alkenyl-, 2-cycloalkyl-, 2-cycloalkylalkyl-, or 2-phenylalkyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolines. Thus, when starting with N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylamine and proceeding as above, there are obtained 2-methyl-, 2-ethyl-, 2-allyl-, 2-cyclopentyl-, 2-cyclohexylmethyl-, and 2-benzyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline, respectively.

When using as starting material an amine of the formula IX in which R represents hydrogen, $R^1$ is as defined immediately above and $R^3$ represents lower alkyl or its hydrochloride salt, and reacting it with formaldehyde, there are obtained the corresponding compounds of formula I in which $R^1$ and $R^3$ are as defined immediately above, viz., the corresponding 1,2-dialkyl-, 1-alkyl-2-alkenyl-, 1-alkyl-2-cycloalkyl-, 1-alkyl-2-cycloalkylalkyl-, or 1-alkyl-2-phenylalkyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolines. In this manner, when starting with N-methyl-, N-ethyl-, N-allyl-, N-cyclopentyl-, N-cyclohexylmethyl-, or N-benzyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine or their respective hydochloride salts there are obtained 1,2-dimethyl-, 1-methyl-2-ethyl-, 1-methyl-2-allyl-, 1-methyl-2-cyclopentyl-, 1-methyl-2-cyclohexylmethyl-, and 1-methyl-2-benzyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, respectively.

When using as starting materials an amine of the formula IX in which R and $R^3$ represent hydrogen and $R^1$ represents alkyl, alkenyl, cycloalkyl, cycloalkylalkyl or phenylalkyl, and reacting it in the manner described above with an aldehyde of the formula $R^2CHO$ in which $R^2$ is as defined immediately above, there are obtained the corresponding compounds of formula I in which $R^1$ and $R^2$ are as defined immediately above and $R^3$ represents hydrogen, viz., the corresponding 2,3-dialkyl-, 2-alkyl-3-alkenyl-, 2-alkyl-3-cycloalkyl-, 2-alkyl-3-cycloalkylalkyl-, 2-alkyl-3-phenyl-, 2-alkyl-3-phenylalkyl-, 2-alkenyl-3-alkyl-, 2,3-dialkenyl-, 2-alkenyl-3-cycloalkyl-, 2-alkenyl-3-cycloalkylalkyl-, 2-alkenyl-3-phenyl-, 2-alkenyl-3-phenylalkyl-, 2-cycloalkyl-3-alkyl-, 2-cycloalkyl-3-alkenyl-, 2,3-di-(cycloalkyl)-, 2-cycloalkyl-3-cycloalkylalkyl-, 2-cycloalkyl-3-phenyl-, 2-cycloalkyl-3-phenylalkyl-, 2-cycloalkylalkyl-3-alkyl-, 2-cycloalkylalkyl-3-alkenyl-, 2-cycloalkylalkyl-3-cycloalkyl-, 2,3-di-(cycloalkylalkyl)-, 2-cycloalkylalkyl-3-phenyl-, 2-cycloalkylalkyl-3-phenylalkyl-, 2-phenylalkyl-3-alkyl, 2-phenylalkyl-3-alkenyl-, 2-phenylalkyl-3-cycloalkyl-, 2-phenylalkyl-3-cycloalkylalkyl-, 2-phenylalkyl-3-phenyl-, or 2,3-di-(phenylalkyl)-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolines.

In this manner, when reacting N-methyl-, N-ethyl-, N-allyl-, N-cyclopentyl-, N-cyclohexylmethyl, or N-benzyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohept-5-yl)methylamine or the hydrochloride salts of the above compounds with acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, n-pentan-1-al, isopentan-1-al (2-methylbutan-1-al), n-hexan-1-al, isohexan-1-al (4-methylpentan-1-al) n-heptan-1-al, n-octan-1-al, n-nonan-1-al, n-undecan-1-al, vinylacetaldehyde, cyclopropyl-

ald hyde, cyclohexylacetaldehyde, benzaldehyd , or phenylacetaldehyde, the following 2,3-disubstituted 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, are respectively obtained:

| Substituent in Position 2 | Substituent in Position 3 |
|---|---|
| 2-methyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexylmethyl-, 3-phenyl-, 3-benzyl- |
| 2-ethyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexylmethyl-, 3-phenyl-, 3-benzyl- |
| 2-allyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexylmethyl-, 3-phenyl-, 3-benzyl- |

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| Substituent in Position 2 | Substituent in Position 3 |
|---|---|
| 2-cyclopentyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexyl-methyl-, 3-phenyl-, 3-benzyl- |
| 2-cyclohexyl-methyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexyl-methyl-, 3-phenyl-, 3-benzyl- |
| 2-benzyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexyl-methyl-, 3-phenyl-, 3-benzyl - |

When using as starting material an amin f f rmula IX in which R represents hydrogen, $R^1$ is as defined immediately above, and $R^3$ represents lower alkyl, and reacting it in the manner described above with an aldehyde of the formula $R^2CHO$ in which $R^2$ is as defined immediately above, there are obtained the compounds of formula I in which R represents hydrogen and $R^1$, $R^2$, and $R^3$ are as defined immediately above, viz.,1,2,3-trialkyl-, 1,2-dialkyl-3-alkenyl-,1,2-dialkyl-3-cycloalkyl-, 1,2-dialkyl-3-cycloalkylalkyl-,1,2-dialkyl-3-phenyl-, 1,2-dialkyl-3-phenylalkyl-, 1,3-dialkyl-2-alkenyl-, 1-alkyl-2,3-dialkenyl-, 1-alkyl-2-alkenyl-3-cycloalkyl-, 1-alkyl-2-alkenyl-3-cycloalkylalkyl-, 1-alkyl-2-alkenyl-3-phenyl-, 1-alkyl-2-alkenyl-3-phenylalkyl-, 1,3-dialkyl-2-cycloalkyl-,1-alkyl-2-cycloalkyl-3-alkenyl-, 1-alkyl-2,3-di-(cycloalkyl)-, 1-alkyl-2-cycloalkyl-3-cycloalkylalkyl-, 1-alkyl-2-cycloalkyl-3-phenyl-, 1-alkyl-2-cycloalkyl-3-phenylalkyl-, 1,3-dialkyl-2-cycloalkylalkyl-, 1-alkyl-2-cycloalkylalkyl-3-alkenyl-,1-alkyl-2-cycloalkylalkyl-3-cycloalkyl-, 1-alkyl-2,3-di(cycloalkylalkyl)-, 1-alkyl-2-cycloalkylalkyl-3-phenyl-, 1-alkyl-2-cycloalkylalkyl-3-phenylalkyl-, 1,3-dialkyl-2-phenylalkyl-, 1-alkyl-2-phenylalkyl-3-alkenyl-, 1-alkyl-2-phenylalkyl-3-cycloalkyl-, 1-alkyl-2-phenylalkyl-3-cycloalkylalkyl-, 1-alkyl-2-phenylalkyl-3-phenyl-, or 1-alkyl-2,3-di-(phenylalkyl)-1,2,3,7,8,12b-hexahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinolines.

In this manner, when reacting N-methyl-, N-ethyl-, N-allyl-, N-cyclopentyl-, N-cyclohexylmethyl- or N-benzyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine or the hydrochloride salts

of the above compounds with acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, n-pentan-1-al, isopentan-1-al (2-methylbutan-1-al), n-hexan-1-al, isohexan-1-al (4-methylpentan-1-al) n-heptan-1-al, n-octan-1-al, n-nonan-1-al, n-undecan-1-al, vinylacetaldehyde, cyclopropylaldehyde, cyclohexylacetaldehyde, benzaldehyde, or phenylacetladehyde there are obtained the following 1,2,3-trisubstituted 1,2,3,7,8,12b- hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinolines, respectively.

| Substituent in Position 1 | Substituent in Position 2 | Substituent in Position 3 |
|---|---|---|
| 1-methyl- | 2-methyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexyl-methyl-, 3-phenyl-, 3-benzyl- |
| 1-methyl- | 2-ethyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexyl-methyl-, 3-phenyl-, 3-benzyl- |
| 1-methyl- | 2-allyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexyl-methyl-, 3-phenyl-, 3-benzyl- |

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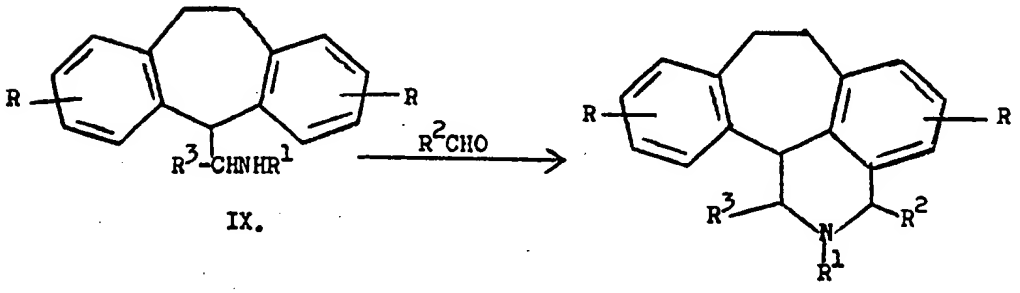
| Substituent in Position 1 | Substituent in Position 2 | Substituent in Position 3 |
|---|---|---|
| 1-methyl- | 2-cyclopentyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexyl-methyl-, 3-phenyl-, 3-benzyl- |
| 1-methyl- | 2-cyclohexyl-methyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexyl-methyl-, 3-phenyl-, 3-benzyl- |
| 1-methyl- | 2-benzyl- | 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexyl-methyl-, 3-phenyl-, 3-benzyl - |

When using as starting material in the above procedure any of the amines of formula IX in which R represents lower alkyl, halogen, hydroxyl, lower alkoxy, lower acyloxy, lower alkylthio, lower alkylsulfonyl, trihalomethyl, amino, lower alkylamino, di-(lower alkyl)aminosulfonyl, or nitro, $R^1$ represents hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, or phenylalkyl, and $R^3$ represents hydrogen or lower alkyl, and reacting it in the manner described above with an aldehyde of the formula $R^2CHO$ in which $R^2$ represents hydrogen, alkyl, alkenyl cycloalkyl, cycloalkylalkyl, phenyl, or phenylalkyl, the corresponding compounds of formula I in which R, $R^1$, $R^2$, and $R^3$ are as defined above are obtained. In this manner, when starting with the 1,2,3 or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1,2, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro, or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine or 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine or their respective N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives, there are obtained, respectively, the 6- or 9, 5- or 10-, 4- or 11-, or 12-methyl, 9,12-dimethyl, 4- or 11-t-butyl, 6- or 9-, 5- or 10- or 4- or 11-chloro, 4- or 11-fluoro, 4- or 11-bromo, 4,10- or 5,11-dibromo, 5- or 10-hydroxy or 4- or 11-hydroxy, 5- or 10-methoxy or 4- or 11-methoxy, 5- or 10-acetoxy, 4- or 11-methylthio,

4- or 11-methylsulfonyl, 4- or 11-trifluoromethyl, 12-amino, 12-methylamino, 4- or 11-dimethylaminosulfonyl, 4-bromo-11-dimethylaminosulfonyl or 11-bromo-4-dimethylaminosulfonyl, 4,11-dinitro and 4,9- or 6,11-dinitro derivatives of the 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolines described earlier in this Application.

Those reactions are shown in the following formulae in which R, $R^1$, $R^2$, and $R^3$ have the significance defined above.




IX. I.

Alternatively, an amine of the formula IX in which R and $R^3$ are as defined in the first instance and $R^1$ represents hydrogen is treated with phosgene in the presence of a strong acid to yield the corresponding isocyanate of the formula XXIV, in which R and $R^3$ are as defined in the first instance identical with the compound obtained from the corresponding 5-alkanoic acid XV through its acid chloride and acid azide as described earlier in this Application. This reaction is carried out in an inert solvent with a molar excess of phosgene at or about room temperature for prolonged periods of time. Preferred

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reacti n conditions include the use of a halogenated hydrocarbon, preferably chlorobenzene or carbon tetrachloride, as the inert solvent, the use of anhydrous hydrogen chloride, reaction temperatures of from about 10°C to about 30°C, and reaction times of from 1-6 hours, the length of the reaction time dependent upon the reaction temperature. Evaporation of excess phosgene and of the solvent yields the desired isocyanate of formula XXIV.

Treatment of said last-named isocyanate of the formula XXIV with a Lewis acid yields the corresponding lactam of formula XXV in which R and $R^3$ are as defined in the first instance and $R^1$ represents hydrogen. This reaction is carried out in an inert solvent, for example a nitrated aromatic hydrocarbon, using a Lewis acid such as, for example a halide of a group III metal, at an elevated temperature above room temperature for prolonged periods of time. Preferred reaction conditions include the use of nitrobenzene as the inert solvent, of aluminium chloride as the Lewis acid, and reaction temperatures within the range of from 20 to 100°C., preferably 60-70°C.

The time of reaction depends upon the preferred temperature and many vary from 0.5 to 6 hours. Addition of water, extraction with a water-immiscible solvent, and evaporation of the latter yields the desired lactam of formula XXV in which R and $R^3$ are as defined in the first instance and $R^1$ represents hydrogen.

Said lactam of formula XXV may als b obtained by tr ating a 5-alkanoic acid of the formula XV in which R and $R^3$ are as defined in the first instance with a cyclizing agent such as, for example, an acid, an acid anhydride, or a Lewis acid, to obtain the corresponding cyclic ketone of formula XXVI in which R and $R^3$ are as defined in the first instance. In this reaction the acid used may be anhydrous hydrogen fluoride or polyphosphoric acid, the acid anhydride may be phosphorous pentoxide, and the Lewis acid may be aluminium chloride . An inert solvent such as, for example, a halogenated hydrocarbon, may also be used. Reaction temperatures of from room temperature to the boiling point of the mixture, and reaction times depending upon the preferred reaction temperature are employed. Preferred conditions include the use of polyphosphoric acid or of anhydrous hydrogen fluoride in the absence of a solvent, reaction temperatures of from room temperature to about 100°C, and reaction times of from 2-24 hours. Optional quenching with ice, extraction with a water-immiscible solvent, washing with aqueous alkali, and evaporation of the solvent yields the desired cyclic ketone of formula XXVI. In this manner, when starting with (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid (XV, R = $R^3$ = H) or with 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid (XV, R = H, $R^3$ = $CH_3$) there are obtained 2-oxo-1,6,7,11b-tetrahydro-2H-dibenzo[cd,h]azulene (XXVI, R = $R^3$ = H) and 1-methyl-2-oxo-1,6,7,11b-tetrahydro-2H-dibenz[cd,h]azulene (XXVI, R = H, $R^3$ = $CH_3$), respectively. When using as starting material any of the 5-alkanoic acids of formula XV in which R is

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other than hydrogen as defined in the first instance, th corr spond-ing dibenz[cd,h]azulene derivatives of formula XXVI in which R has the significance other than hydrogen defined in the first instance is obtained.

Treatment of said last-named cyclic ketone of formula XXVI in which R and $R^3$ are as defined in the first instance with hydrazoic acid yields the corresponding lactam of formula XXV in which R and $R^3$ are as defined in the first instance and $R^1$ represents hydrogen. In this reaction, the hydrazoic acid may be prepared in situ from a suitable acid and a suitable metal azide. The reaction may be carried out at an elevated temperature above room temperature for periods of time of from a few minutes to several hours. Preferred reaction conditions include the use of molten trichloroacetic acid and sodium azide for the preparation of hydrazoic acid in situ, heating for 10-60 minutes on a steam bath, and allowing the reaction to come to completion by standing at room temperature for 12-48 hours. Quenching with water, making the mixture alkaline, extraction with a water-immiscible solvent, preferably a halogenated hydrocarbon, and evaporation of the solvent yields the desired lactam of formula XXV in which R and $R^3$ are as defined in the first instance and $R^1$ represents hydrogen.

In this manner, when starting with an amine of formula IX in which $R^1$ is hydrogen and R and $R^3$ are as defined in the first instance, for example (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (IX, R = $R^1$ = $R^3$ = H) or 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine, or with a 5-alkanoic

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acid of formula XV in which R and $R^3$ are as defined in the first instance, for example (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid (XV, R = $R^3$ = H) or 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid (XV, R = H, $R^3$ = $CH_3$), or with any of the derivatives of the above compounds of formulae IX or XV in which R is other than hydrogen, there are obtained, respectively, 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-one (XXV, R = $R^1$ = $R^3$ = H), 1-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolin-3-one (XXV, R = $R^1$ = H, $R^3$ = $CH_3$), and their derivatives of formula XXV in which R is other than hydrogen as defined in the first instance.

The lactam of formula XXV in which R and $R^3$ are as defined in the first instance and $R^1$ represents hydrogen is treated with a reducing agent to obtain the corresponding compound of formula I in which R and $R^3$ are as defined in the first instance and $R^1$ and $R^2$ both represent hydrogen, viz., 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline or 1-alkyl-, for example 1-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline or their analogues with nuclear substituents. This reaction may be carried out in an inert solvent such as, for example, an ether or a cyclic ether, with a complex alkali metal aluminum hydride as the reducing agent, at temperatures of from about room temperature to the boiling point of the mixture and for prolonged periods of time depending upon the preferred reaction temperature. Preferred conditions include the use of tetrahydrofuran as the

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solvent, of lithium aluminum hydride as the reducing agent, of reaction temperatures at or near the boiling point of the mixture, and reaction times of from 12-24 hours. Addition of water, filtration of inorganic salts, and evaporation of the solvent yields the desired compound of formula I in which R and $R^3$ are as defined in the first instance and $R^1$ and $R^2$ both represent hydrogen, identical with the compounds of the same formula described earlier in this Application.

When it is desired to prepare compounds of formula I in which R and $R^3$ are as defined in the first instance, $R^1$ is alkyl, alkenyl, cycloalkyl, cycloalkylalkyl or phenylalkyl, and $R^2$ is hydrogen, a lactam of formula XXV in which R and $R^3$ are as defined in the first instance and $R^1$ is hydrogen is treated with an alkylating agent of the formula $R^1Z$ in which $R^1$ is as defined immediately above and Z represents a leaving group capable of bearing a pair of electrons, such as a halogen with an atomic weight greater than 19, a tosyloxy, or a mesyloxy group, in the presence of a basic condensing agent such as an alkali metal hydroxide, alkoxide, or hydride, in the optional presence of an inert solvent and at an elevated temperature above room temperature. The nature of the alkylating agent will determine the type of solvent and the reaction conditions used. For example, when $R^1Z$ represents an alkyl halide, the latter may serve as solvent or a lower alkanol may be used as solvent; the condensing agent in this case may be an alkali metal

lower alkoxide; and the reaction may be carried out at the reflux temperature of the mixture, if necessary in a closed vessel under pressure, for periods of time of from one to several hours. Other alkylating agents of the formula $R^1Z$ in which $R^1$ and Z are as defined immediately above may require more drastic conditions, as will be apparent to those skilled in the art. Preferred reaction conditions include the use of a molar excess of the alkylating agent, of an inert solvent, of sodium or potassium hydroxide, alkoxide, or hydride as the condensing agent, and of reaction temperatures from room temperature to the reflux temperature of the mixture under the prevailing pressure.

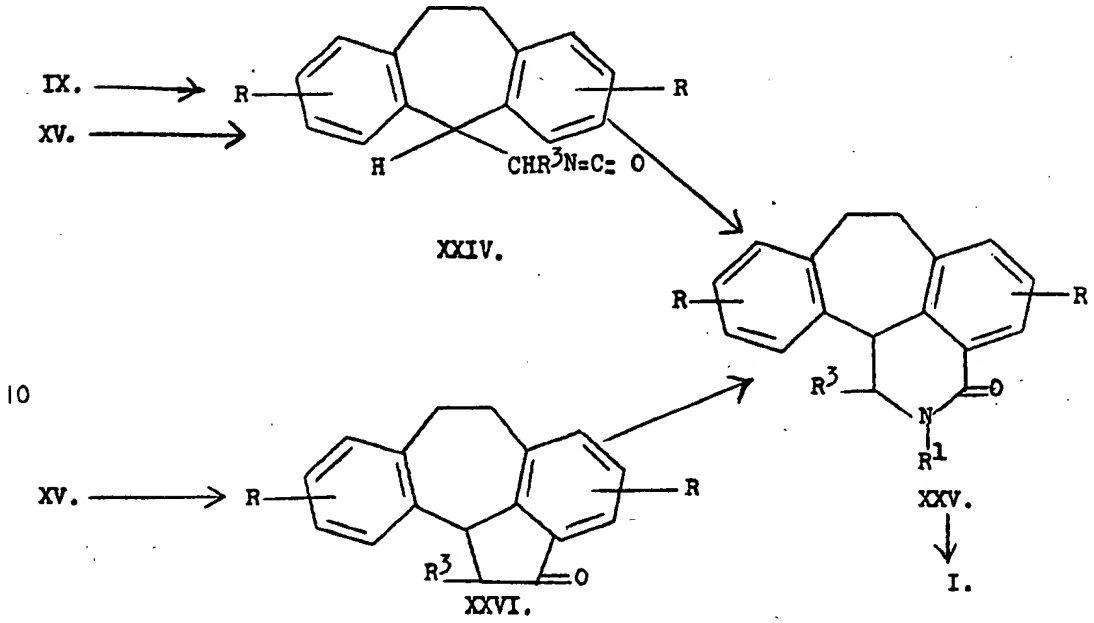
Alternatively, the above lactam may also be treated with an acid anhydride of the formula $R^4COOOCR^4$ or with an acyl halide of the formula $R^4COX$ in which $R^4$ is $R^1$ minus $CH_2$ and X represents a halogen with an atomic weight greater than 19, in the presence of a basic condensing agent such as for example, an organic base which may also serve as the solvent, at an elevated temperature above room temperature and for prolonged periods of time. Preferred reaction conditions include the use of a molar excess of the acyl halide, of pyridine or dimethylaniline as the condensing agent, of temperatures from room temperature to the reflux temperature of the mixture, and of reaction times of from 1-48 hours.

There are thus obtained N-alkylated or N-acylated derivatives of the lactams of formula XXV, i.e. compounds of

f rmula XXV in which R and $R^3$ are as defined in the first instance and $R^1$ is alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, phenylalkyl, or an acyl group of the formula $R^4CO$ in which $R^4$ is $R^1$ minus $CH_2$. In this manner, when using as starting material 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-one and reacting it with methyl iodide, ethyl iodide, allyl bromide, cyclopentyl bromide, cyclohexylmethyl chloride, benzyl chloride, acetic anhydride or acetyl chloride, there are obtained 1-methyl-, 1-ethyl-, 1-allyl-, 1-cyclpentyl-, 1-cyclohexylmethyl-, 1-benzyl-, or 1-acetyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolin-3-one, respectively.

These last-named compounds are treated with a reducing agent such as a complex alkali metal aluminum hydride in an inert solvent such as an ether or cyclic ether, in the manner described above, to yield the corresponding compounds of formula I. In this process it is not only the lactam group which is reduced but any acyl group present is also reduced. Preferred reaction conditions include the use of lithium aluminum hydride in tetrahydrofuran as the solvent, at the reflux temperature of the mixture for periods of time of from 1-24 hours. Addition of water, filtration of inorganic salts, extraction with an organic solvent, and evaporation of the latter yields the corresponding compounds of formula I in which R and $R^3$ are as defined in the first instance, $R^1$ is alkyl, e.g. methyl or ethyl; alkenyl, e.g. allyl; cycloalkyl, e.g. cyclopentyl; cycloalkylalkyl, e.g. cyclohexylmethyl; or phenylalkyl e.g. benzyl; and $R^2$ is hydrogen; identical with the same compounds obtained by other means as described earlier in this Application.

Those reactions are shown in the following formulae in which R, $R^1$, $R^2$ and $R^3$ have the significance defin d above




In another alternative of the process outlined above an amine of formula IX in which R, $R^1$ and $R^3$ are as defined in the first instance is treated with a formylating agent such as, for example formic acetic anhydride, chloral, formic acid, or a lower alkyl formate, to obtain the corresponding amine of formula XXVII(a) in which Y represents the formyl group. This reaction is usually carried out with a molar excess of the formylating agent which may also be used as a solvent, at temperatures between about 0°C and 100°C. Preferred reaction conditions include the use of formic acetic anhydride, previously prepared by heating formic acid and acetic anhydride together for several hours at 50-60°C, of

reaction temperatures at about room temperature, and of reaction times of from 2-24 hours. Quenching with water, xtraction with a water-immiscibl solvent, preferably ethyl ac tate, washing with alkali and evaporation of the solv nt yields the amine of formula XXVII(a) in which R, $R^1$ and $R^3$ are as defined in the first instance and Y represents the group $COR^2$ in which $R^2$ represents hydrogen, viz., the formyl group. In this manner, when starting with (10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)-methylamine (IX, R = $R^1$ = $R^3$ = H) or with 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (IX, R = $R^1$ = H, $R^3$ = $CH_3$) or with any of their N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives, there are obtained the corresponding N-formyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine(XXVII(a), R = $R^1$ = $R^3$ = H, Y = CHO), N-formyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (XXVII(a), R = $R^1$ = H, $R^3$ = $CH_3$, Y = CHO) and their respective N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexyl-methyl, and N-benzyl derivatives. When using as starting material any of the above amines of formula IX in which R is other than hydrogen as defined in the first instance, there are obtained the corresponding amines of formula XXVII(a) in which $R^1$, $R^3$ and Y are as defined immediately above and R has the significance other than hydrogen defined in the first instance.

The N-formyl derivatives of formula XXVII(a) in which R and $R^3$ are as defined in the first instance, Y is CHO, and $R^1$ is hydrogen are also obtained by treating the corresponding isocyanate of formula XXIV, preferably in solution in an aromatic hydrocarbon and at -20°C to 50°C, with formic acid.

Alternatively, the amine of formula IX in which R, $R^1$ and $R^3$ are as defined in the first instance is treated with an acylating agent such as an acid halide of the formula

$R^2COX$ in which $R^2$ is alkyl, alkenyl, (lower alkoxy)alkyl, cycloalkyl, cycloalkylalkyl, phenyl, or phenylalkyl and X represents a halogen with an atomic weight greater than 19, or with an acid anhydride of the formula $R^2COOOCR^2$ in which $R^2$ is as defined immediately above, to obtain the corresponding amine of formula XXVII(b) in which Y represents the group $COR^2$ in which $R^2$ is as defined immediately above. This reaction is carried out in the presence of a basic condensing agent which may also serve as solvent, at temperatures between room temperature and the reflux temperature of the mixture, and for prolonged periods of time depending upon the preferred reaction temperature. Preferred conditions include the use of molar excess of an acid anhydride of the formula $R^2COOOCR^2$ in which $R^2$ is as defined immediately above, the use of pyridine as basic condensing agent and solvent, reaction temperatures of from 50°C to the boiling point of the mixture, and reaction times of from 6-24 hours. Evaporation of the solvent, extraction with a water-immiscible solvent, preferably chloroform, washing with water and evaporation of the solvent yields the corresponding amine of formula XXVII(b) in which R, $R^1$ and $R^2$ are as defined in the first instance and Y represents the group $COR^2$ in which $R^2$ is alkyl, alkenyl, (lower alkoxy)alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl. In this manner, when starting with (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (IX, R = $R^1$ = $R^3$ = H), 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (IX, R = $R^1$ = H, $R^3$ = $CH_3$), or with their N-methyl, N-ethyl, N-allyl,

N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives, or with any of their derivatives or formula IX in which R is other than hydrogen as defined in the first instance, and reacting with acetic acid, propionic acid, butyric acid, isobutyric acid, pentanoic acid, isopentanoic acid, hexanoic acid, isohexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, undecanoic acid, propenoic acid, methoxyacetic acid, cyclopropylcarboxylic acid, cyclohexylacetic acid, benzoic acid, or phenylacetic acid chloride or anhydride, there are respectively obtained the N-acetyl, N-propionyl, N-butanoyl, N-isobutanoyl,N-pentanoyl, N-isopentanoyl, N-hexanoyl, N-isohexanoyl, N-heptanoyl, N-octanoyl, N-nonanoyl, N-undecanoyl, N-propenoyl, N-methoxyacetyl, N-cyclopropylcarbonyl, N-cyclohexylacetyl, N-benzoyl, and N-phenylacetyl derivatives of (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylamine, (XXVII(b), $R = R^1 = R^3 = H$, Y = acyl as listed above)1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (XXVII(b), $R = R^1 = H$, $R^3 = CH_3$, Y = acyl as listed above) and the N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, and N-benzyl derivatives of the compounds listed above as well as their derivatives of formula XXVII(b) in which R has the significance other than hydrogen defined in the first instance.

In still another alternative, an amine of formula IX in which R, $R^1$, and $R^3$ are as defined in the first instance is treated with a lower alkyl haloformate to obtain the corresponding amine of formula XXVII(c) in which Y represents the group COO(lower alkyl). This reaction is carried out in an inert

solvent in the presence of a basic condensing agent, at temperatures below room temperature, and for periods of time of from a few minutes to several hours. Preferred conditions include the use of ethyl chloroformate, of a halogenated hydrocarbon and as, for example, ethylene dichloride as the inert solvent, of sodium hydroxide as the basic condensing agent, of reaction temperatures between 0°C and room temperature, and of reaction times of from 15 minutes to 2 hours. In this manner there are obtained the corresponding amines of formula XXVII(c) in which R, $R^1$ and $R^3$ are as defined in the first instance and Y represents the group COO(lower alkyl). In this manner, when starting with (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (IX, R = $R^1$ = $R^3$ = H), 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (IX, R = $R^1$ = H, $R^3$ = $CH_3$), or with their N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives, or with any of their derivatives of formula IX in which R is other than hydrogen as defined in the first instance, and reacting with ethyl chloroformate, there are respectively obtained N-carbethoxy-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (XXVII(c), R = $R^1$ = $R^3$ = H, Y = $COOC_2H_5$), N-carbethoxy-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (XXVII(c), R = $R^1$ = H, $R^3$ = $CH_3$, Y = $COOC_2H_5$), the N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl and N-benzyl derivatives of the above compounds, and the corresponding compounds of formula XXVII(c) in which R has the significance other than hydrogen defined in the first instanc .

Said last-named amines of formula XXVII(c) are treated with a cyclizing agent such as an acid, an acid anhydride together with an acid halide, or a Lewis acid to obtain the corresponding lactams of formula XXV. It should be noted that the methods for preparing said lactams of formula XXV described earlier in this Application permitted only the obtention of such lactams in which $R^1$ is hydrogen, and that the substituent $R^1$ had to be introduced by subsequent steps, also described earlier in this Application. The method of cyclizing an amine of the formula XXVII(c) in which Y represents the group COO(lower alkyl) and $R^1$ is as defined in the first instance now permits the preparation of lactams of the formula XXV in which $R^1$ is not only hydrogen but also alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, or phenylalkyl. Such cyclization is carried out with an acid such as, for example polyphosphoric acid, with an acid anhydride together with an acid halide such as, for example, a mixture of phosphorus pentoxide and phosphorus oxychloride, or with a Lewis acid such as, for example, aluminum chloride; when using an acid as the cyclizing agent it is conducted in the absence of solvent, and when using one of the other cyclizing agents described above an inert solvent such as a hydrocarbon or a halogenated hydrocarbon is used; the reaction temperature depends upon the nature of the cyclizing agent and may vary from room temperature to the boiling pount of the mixture, with reaction times of from one to several hours. Preferred

conditions include the use of polyphosphoric acid at 100-200°C for 1-4 hours, or of a mixtur of phosphorus pentoxide and phosphorus oxychloride (1:2) in xylene, at the reflux temperature of the mixture, for 1-4 hours. Optional quenching with water, extraction with a water-immiscible solvent, washing with alkali, and evaporation of the solvent yields the corresponding lactam of formula XXV in which R, $R^1$ and $R^3$ are as defined in the first instance.

In this manner, when starting with N-carbethoxy-10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)-methylamine (IX, R = $R^1$ = $R^3$ = H), N-carbethoxy-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (IX, R = $R^1$ = H, $R^3$ = $CH_3$), or with their N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives, or with any of their derivatives of formula IX in which R is other than hydrogen as defined in the first instance, and reacting with polyphosphoric acid, a mixture of phosphorus pentoxide and phosphorus oxychloride, or aluminum chloride, there are respectively obtained 1,2,3,7,8,12b-hexahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinolin-3-one (XXV, R = $R^1$ = $R^3$ = H) 1-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolin-3-one (XXV, R = $R^1$ = H, $R^3$ = H), their 2-methyl, 2-ethyl, 2-allyl, 2-cyclopentyl, 2-cyclohexylmethyl, and 2-benzyl derivatives, and the lactams of formula XXV in which R has the significance other than hydrogen defined in the first instance. Treatment of said last-named lactams with a reducing agent in the manner described earlier in this Application yields the corresponding compounds of formula I in which R, $R^1$ and $R^3$ are as defined in the first instanc and $R^2$ is hydrog n,

also describ d earlier in this Application.

Alternatively, an amine of formula XXVII (a) or (b) in which R and $R^3$ are as defined in the first instance, $R^1$ is hydrogen, and Y is (a) CHO or (b) $COR^2$ in which $R^2$ is alkyl, alkenyl, (lower alkoxy)alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl is treated with a cyclizing agent such as an acid or a Lewis acid to obtain the corresponding Schiff base of the formula XXVIII in which R, $R^2$ and $R^3$ are as defined in the first instance. Said cyclization is carried out in the same manner as described above. Preferred conditions include the use of polyphosphoric acid without any other solvent, at temperatures of from 100-200°C for 0.5-3 hours; quenching with ice, extraction with a water-immiscible solvent, optional washing with alkali, and evaporation of the solvent yields the corresponding Schiff base of formula XXVIII in which R, $R^2$ and $R^3$ are as defined in the first instance.

In this manner, when starting with the compounds of formulae XXVII(a) or XXVII(b) N-formyl-, N-acetyl-, N-propionyl-, N-butanoyl-, N-isobutanoyl-, N-pentanoyl-, N-isopentanoyl-, N-hexanoyl-, N-isohexanoyl-, N-heptanoyl-, N-octanoyl-, N-nonanoyl-, N-undecanoyl-, N-propenoyl-, N-methoxyacetyl-, N-cyclopropylcarbonyl-, N-cyclohexylacetyl-, N-benzoyl-, or N-phenylacetyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, or -1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine and treating any of said compounds with polyphosphoric acid, there are obtained, respectively, the Schiff bases of formula XXVIII 1,7,8,12b-tetra-

hydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline (XXVIII, R = $R^2$ = $R^3$ = H), 1-m thyl-1,7,8,12b-t trahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (XXVIII, R = $R^2$ = H, $R^3$ = $CH_3$) and their respective 3-methyl, 3-ethyl, 3-propyl, 3-isopropyl, 3-butyl, 3-isobutyl, 3-anyl, 3-isoanyl, 3-hexyl, 3-heptyl, 3-octyl, 3-decyl, 3-allyl, 3-methoxymethyl, 3-cyclopropyl, 3-cyclohexylmethyl, 3-phenyl, and 3-benzyl derivatives. When using as starting materials the derivatives of the above compounds of formulae XXVII(a) or XXVII(b) in which R is other than hydrogen as defined in the first instance, the correspondingly substituted derivatives of the Schiff bases of formula XXVIII in which R has the significance other than hydrogen defined in the first instance are obtained.

Said last-named Schiff base of formula XXVIII in which R, $R^2$ and $R^3$ are as defined in the first instance is treated with a reducing agent to obtain the corresponding compound of formula I in which R, $R^2$ and $R^3$ are as defined in the first instance and $R^1$ is hydrogen. Said reduction is carried out with a complex alkali metal aluminum hydride in an inert solvent such as an ether or a cyclic ether or an alkali metal borohydride in a lower alkanol, at an elevated temperature above room temperature, or with hydrogen in the presence of a noble metal catalyst at or about room temperature, for periods of time of from 2-48 hours. Preferred conditions include the use of lithium aluminum hydride in tetrahydrofuran, or of sodium borohydride in ethanol, at the reflux temperature of the mixture, for 4-24 hours. Addition of water, optional

filtration of inorganic salts, extraction with a water-immiscible solvent and vaporation of th solv nt yields the corresponding compound of formula I in which R, $R^2$ and $R^3$ are as defined in the first instance and $R^1$ is hydrogen as described earlier in this Application, as well as the 3-methoxymethyl derivative of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinoline and of its 1-methyl derivative which may conveniently be obtained in this manner.

When it is desired to obtain compounds of formula I in which R and $R^3$ are as defined in the first instance, $R^2$ is hydrogen, and $R^1$ is alkyl, cycloalkyl, cycloalkylalkyl, or phenylalkyl, the corresponding Schiff base of formula XXVIII is treated with Raney nickel in the presence of a compound of the formula $R^1OH$ in which $R^1$ is as defined immediately above, preferably under anhydrous conditions and at temperatures of from 50°C to the boiling point of the mixture.

In a reversal of the reaction described immediately above, a compound of formula I in which R, $R^2$ and $R^3$ are as defined in the first instance and $R^1$ is hydrogen is treated with an oxidizing agent such as, for example an alkali metal hypohalite, mercuric chloride or acetate, or manganese dioxide, to obtain the corresponding Schiff base of formula XXVIII. Such oxidation is preferably carried out with sodium hypochlorite at temperatures between 0°C and room temperature. Extraction with a water-immiscible solvent and evaporation gives the Schiff base of formula XXVIII in which R, $R^2$ and $R^3$ are as defined in the first instance.

In a variant of the above procedure, a Schiff base of formula XXVIII in which R and $R^3$ are as defined in the first instance and $R^2$ represents hydrogen is treated with a Grignard reagent of the formula $R^2MgX$ or a lithium or cadmium d rivative of the formula $R^2Li$ or $(R^2)_2Cd$ in which $R^2$ is alkyl, alkenyl, (lower alkoxy)alkyl, cycloalkyl, cycloalkylalkyl, phenyl, or phenylalkyl and X is a halogen with an atomic weight greater than 19, to obtain the corresponding compound

of formula I. This reaction is carried out under the usual conditions f the Grignard reaction, i.e. in an ether or cyclic ether as the solvent, at temperatures above room temperature, and for periods of time of from 1-24 hours. Preferred conditions include the use of diethyl ether or of tetrahydrofuran as the solvent, and carrying out the reaction at the reflux temperature of the mixture for 2-12 hours. Decomposition with ammonium chloride, extraction with a water-immiscible solvent, washing, and evaporation of the solvent yields the corresponding compound of formula I in which R and $R^3$ are as defined in the first instance, $R^2$ is as defined immediately above and $R^1$ is hydrogen described earlier in this Application.

In still another alternative, an amine of the formula XXVII (b) in which R and $R^3$ are as defined in the first instance, $R^1$ is alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, or phenylalkyl and Y represents the group $COR^2$ in which $R^2$ is as defined in the first instance is treated with an acidic dehydrating agent, such as, for example, polyphosphoric acid, phosphorus oxychloride, phosphorus pentoxide, polyphosphoric ester, or mixtures thereof, to obtain the corresponding quaternary Schiff base phosphate salts of formula XXIX in which R, $R^1$, $R^2$, and $R^3$ are as defined above and $Z^-$ represents the phosphate ion. This reaction is carried out with the reagents and under the conditions of the Bischler-Napieralski reaction described, for example, in "Organic Reactions" Vol. 6, p. 74, John Wiley & Sons, Inc.,

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New York 1951. Preferred reaction conditions include the use of phosphorus oxychloride as the acidic dehydrating agent, of an aromatic hydrocarbon such as benzene or toluene as the solvent, of temperatures within the range of 50-150°C, and of reaction times of from 1-12 hours. Addition of an aliphatic hydrocarbon, preferably hexane, and filtration of the resulting precipitate yields the corresponding quaternary Schiff base salt of formula XXIX in which R, $R^2$, and $R^3$ are as defined in the first instance, $R^1$ is alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl, or phenylalkyl, and $Z^-$ is the phosphate ion.

In this manner, when starting with the compounds of formula XXVII (b) viz., the N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives of N-formyl-, N-acetyl-, N-propionyl-, N-butanoyl-, N-isobutanoyl-, N-pentanoyl-, N-isopentanoyl-, N-hexanoyl-, N-isohexanoyl-, N-heptanoyl-, N-octanoyl-, N-nonanoyl-, N-undecanoyl-, N-propenoyl-, N-methoxyacetyl-, N-cyclopropylcarbonyl-, N-cyclohexylacetyl-, N-benzoyl-, or N-phenylacetyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine or -1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine and treating with phosphorus oxychloride there are obtained, respectively, the quaternary Schiff bases of the formula XXIX 2-methyl-, 2-ethyl, 2-allyl, 2-cyclopentyl-, 2-cyclohexylmethyl, and 2-benzyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolinium phosphate (XXIX, R = $R^2$ = $R^3$ = H, $R^1$ = methyl, ethyl, allyl, cyclopentyl, cyclohexylmethyl, and benzyl), 1,2-dimethyl-, 1-methyl-2-ethyl-,

1-methyl-2-allyl-, 1-m thyl-2-cyclopentyl-, 1-methyl-2-cyclohexyl-methyl-, and 1-methyl-2-benzyl-1,7,8,12b-tetrahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinolinium phosphate (XXIX, R = $R^2$ = H, $R^3$ = $CH_3$, $R^1$ = methyl, ethyl, allyl, cyclopentyl, cyclohexylmethyl, and benzyl), and their respective 3-methyl, 3-ethyl, 3-propyl, 3-isopropyl, 3-butyl, 3-isobutyl, 3-amyl, 3-isoamyl, 3-hexyl, 3-heptyl, 3-octyl, 3-decyl, 3-allyl, 3-methoxymethyl, 3-cyclopropyl, 3-cyclohexylmethyl, 3-phenyl, and 3-benzyl derivatives. When using as starting material any of the amines of formula XXVII(b) in which R is other than hydrogen as defined in the first instance, there are obtained the corresponding quaternary Schiff bases of formula XXIX in which R has the significance other than hydrogen defined in the first instance in the form of their phosphate salts.

Said last-named quaternary Schiff base of formula XXIX may also be obtained by treating a Schiff base of formula XXVIII in which R, $R^2$ and $R^3$ are as defined in the first instance described earlier in this Application with an alkylating agent of the formula $R^1Z$ in which $R^1$ is alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, or phenylalkyl and Z is a leaving group capable of bearing a pair of electrons, in solution in an inert solvent such as, for example, a lower ketone, at temperature of from room temperature to the reflux temperature of the mixture, and for periods of time of from 2-48 hours. Preferred conditions include the use of alkylating agents of the formula $R^1Z$ in which $R^1$ is as defined immediately above and Z is a halogen with an atomic weight greater than 19, or the sulfate group, of acetone as the

solvent, of t mperatur s between room temperature and the reflux temperature of the mixture, and of reaction times of from 2-24 hours. In this manner the quaternary Schiff bases of formula XXIX in which R, $R^2$ and $R^3$ are as defined in the first instance and $R^1$ and $Z^-$ are as defined immediately above are also obtained. In this manner, when using as starting materials the Schiff bases of formula XXVIII 1,7,8,12b-tetrahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinoline, 1-methyl-1,7,8,12b-tetrahydro-benzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, or their respective 3-methyl, 3-ethyl, 3-propyl, 3-butyl, 3-isobutyl, 3-amyl, 3-isoamyl, 3-hexyl, 3-heptyl, 3-octyl, 3-decyl, 3-allyl, 3-methoxymethyl, 3-cyclopropyl, 3-cyclohexylmethyl, 3-phenyl, or 3-benzyl derivatives, and reacting any of them with methyl, ethyl, allyl, cyclopentyl, cyclo-hexylmethyl, or benzyl chloride, bromide, iodide, or sulfate there are obtained the same quaternary Schiff bases of formula XXIX as described in the preceding paragraph in the form of their respective chloride, bromide, iodide, or sulfate salts. When using as starting material any of the Schiff bases of formula XXVIII in which R is other than hydrogen or defined in the first instance, there are obtained the corresponding quaternary Schiff bases of formula XXIX in which R has the significance other than hydrogen defined in the first instance.

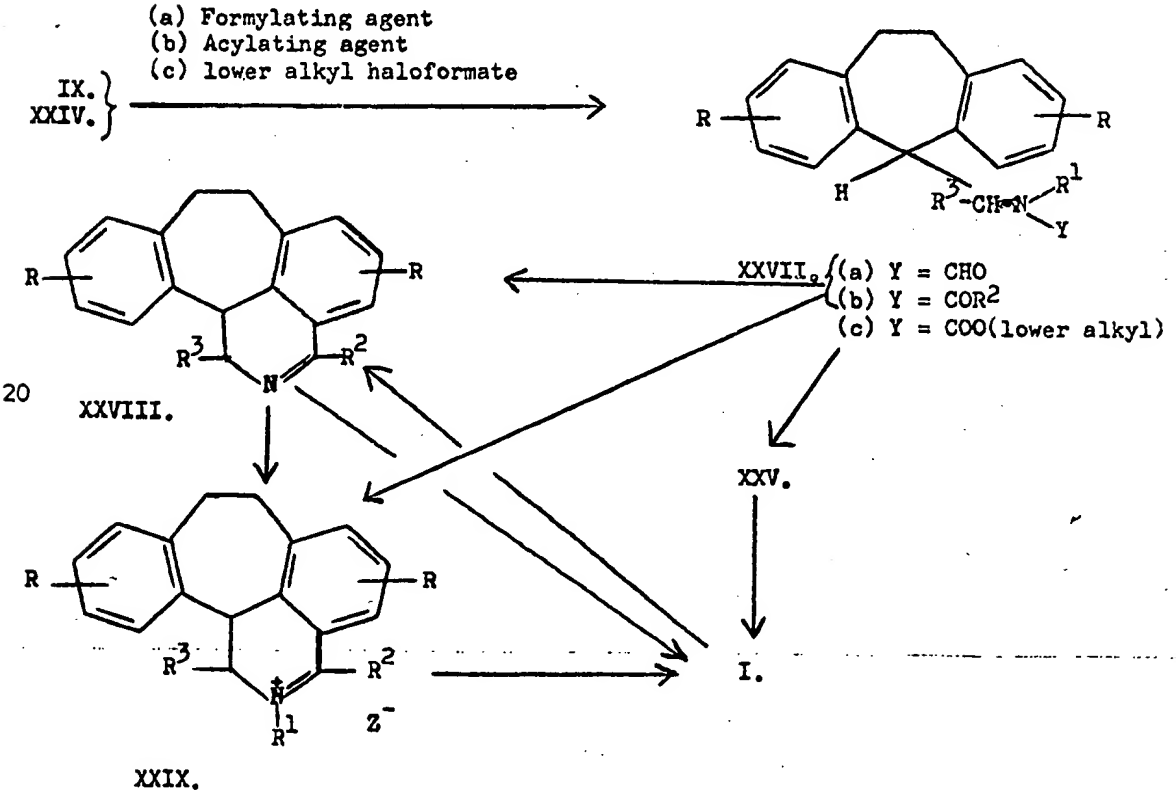
Said last-named quaternary Schiff base of formula XXIX is treated with a reducing agent in the same manner as described above for the Schiff base of formula XXVIII, i.e. with a complex alkali metal aluminum hydride in an inert solvent such as an ether or a cyclic ether or with an alkali m tal borohydrid in solution in a lower alkanol, at

temperatures between room temperature and the reflux temperature of the mixture and for periods of time of from 2-48 hours, to yield the corresponding compound of formula I. Preferred reaction conditions include the use of sodium borohydride in ethanol, at the reflux temperature of the mixture for periods of time of from 4-24 hours. Addition of water, extraction with a water-immiscible solvent, preferably a halogenated hydrocarbon such as, for example chloroform, and evaporation of the solvent yields the corresponding compound of formula I in which R, $R^2$ and $R^3$ are as defined in the first instance and $R^1$ is alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, phenyl, or phenylalkyl described earlier in this Application.

Alternatively, said quaternary Schiff base of formula XXIX in which R and $R^3$ are as described in the first instance, $R^1$ is as defined immediately above and $R^2$ represents hydrogen is treated with a Grignard reagent of the formula $R^2MgX$ in which $R^2$ is alkyl, alkenyl, (lower alkoxy)alkyl, cycloalkyl, cycloalkylalkyl, phenyl, or phenylalkyl and X represents a halogen with an atomic weight greater than 19 in the same manner as described above for the corresponding Schiff base of formula XXVIII, to obtain the corresponding compound of formula I. Preferred conditions include the use of an ether such as diethyl ether or of a cyclic ether such as tetrahydrofuran as the solvent, of

temperatures between room temperature and the reflux t mperature of the solvent, and of reaction times of from 2-24 hours. Decomposition with ammonium chloride, extraction with a water-immiscible solvent, preferably diethyl ether, and evaporation of the solvent yields the corresponding compound of formula I in which R and $R^3$ are as defined in the first instance, $R^1$ is alkyl, alkenyl, cycloalkyl, cycloalkyl-alkyl, or phenylalkyl and $R^2$ is as defined immediately above described earlier in this Application.

Those reactions are shown in the following formulae in which R, $R^1$, $R^2$ and $R^3$ are as defined in the first instance and Z is as defined above.



The pathways for obtaining the compounds of formula I in which R, $R^1$, $R^2$ and $R^3$ ar as defined in the first instance and may be present in any given combination having thus been described, it should be noted that it may in certain cases be more economical to prepare a compound of formula I in which $R^1$ is hydrogen, and to introduce a substituent $R^1$ into such a compound. This may be achieved by any of the methods for N-substitution described, for example, in Houben-Weyl, Methoden der Organischen Chemie, Georg Thieme Verlag, Stuttgart 1957, and some of these methods will be described below.

A compound of formula I in which R, $R^2$ and $R^3$ are as defined in the first instance and $R^1$ is hydrogen is treated with an alkylating agent of the formula $R^1Z$ in which $R^1$ is alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, or phenylalkyl and Z is a leaving group such as a halogen with an atomic weight greater than 19, a tosyloxy group, or a mesyloxy group, in the presence of a basic condensing agent, in an inert solvent, at an elevated temperature above room temperature which depends upon the nature of the substituent to be introduced, and for periods of time of from 1-48 hours. Preferred conditions include the use of an alkali metal hydride such as, for example, sodium hydride, of an alkali metal hydroxide such as sodium or potassium hydroxide, or of an alkali metal carbonate such as sodium or potassium carbonate as the basic condensing agent, of a lower alkanol such as ethanol as the solvent, of temperatures between 30°C and the reflux temperature of the mixture, and of reaction

times of from 2-24 hours. Addition f water, extraction with a water-immiscible solvent, and evaporation of the solvent yields the corresponding compound of formula I in which R, $R^2$ and $R^3$ are as defined in the first instance and $R^1$ is alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, or phenylalkyl described earlier in this Application.

Alternatively, a compound of formula I in which R, $R^2$ and $R^3$ are as described in the first instance and $R^1$ is hydrogen is treated with an acylating agent, such as an acid anhydride of the formula $R^4COOOCR^4$ or an acid halide of the formula $R^4COX$ in which X is a halogen with an atomic weight greater than 19 and $R^4$ is $R^1$ minus $CH_2$ wherein $R^1$ is alkyl, alkenyl, cycloalkylalkyl or phenylalkyl, in the presence of a basic condensing agent, at temperatures between room temperature and the reflux temperature of the mixture and for periods of time of from 2-48 hours. Preferred conditions include the use of pyridine as the basic condensing agent, at temperatures between 50 and 100°C, for 4-24 hours. Quenching with water, addition of alkali, extraction with a water-immiscible solvent, and evaporation of the solvent yields the corresponding compound of formula I in which R, $R^2$ and $R^3$ are as defined above and $R^1$ is the group $R^4CO$, in which $R^4$ is $R^1$ minus $CH_2$. Said last-named compound is treated with a reducing agent, preferably lithium aluminum hydride or diborane, in an inert solvent preferably an ether or a cyclic ether such as tetrahydrofuran; quenching with water or acid, making the mixture alkaline, extraction with a water-immiscible solvent, and evaporation of th solv nt yields the c rresponding compound

of formula I in which R, $R^2$ and $R^3$ ar as d fined in th first instance and $R^1$ is alkyl, alkenyl, cycloalkylalkyl or phenylalkyl described earlier in this Application. In the special case where it is desired to obtain the compounds of formula I in which R, $R^2$, and $R^3$ are as defined in the first instance and $R^1$ is methyl, a compound of formula I in which R, $R^2$ and $R^3$ are as defined in the first instance and $R^1$ is hydrogen is treated with ethyl chloroformate in the presence of a basic condensing agent such as an alkali metal hydroxide and of a solvent such as a halogenated hydrocarbon, to yield the corresponding compound of formula I in which $R^1$ represents the carbethoxy group. Preferred reaction conditions include the use of sodium hydroxide as the basic condensing agent and of ethylene dichloride as the solvent. The resulting compound of formula I in which $R^1$ represents the carbethoxy group is treated with a reducing agent, preferably lithium aluminium hydride, in the same manner as described above, to yield the corresponding compound of formula I in which R, $R^2$ and $R^3$ are as defined in the first instance and $R^1$ is methyl, also described earlier in this Application.

In another alternative, a compound of formula I in which R, $R^2$ and $R^3$ are as defined in the first instance and $R^1$ is hydrogen is treated with an aldehyde of the formula $R^4CHO$ in which $R^4$ is $R^1$ minus $CH_2$ wherein $R^1$ is alkyl, alkenyl, cycloalkylalkyl or phenylalkyl, followed by treatment with a reducing agent. In the special case where $R^1$ is methyl or ethyl, the aldehyde used is formaldehyde or acetaldehyde and

the reducing ag nt is formic acid, in all other cases the preferred reducing agent is catalytically activated hydrogen, preferably in the presence of a noble metal catalyst. The reaction is carried out in an inert solvent, preferably a lower alkanol, at temperatures between room temperature and the reflux temperature of the mixture. When using hydrogen and a catalyst as the reducing agent it is preferred to work in a closed system at an elevated pressure above atmospheric pressure. When using formic acid as the reducing agent the reaction is quenched with water, made alkaline, extracted with a water-immiscible solvent, and the solvent evaporated. When using hydrogen and a catalyst the latter is filtered and the solvent evaporated. In both cases there are obtained the corresponding compounds of formula I in which R, $R^2$ and $R^3$ are as defined in the first instance and $R^1$ is alkyl, alkenyl, cycloalkylalkyl, or phenylalkyl described earlier in this Application.

Having thus described a number of different pathways by which the compounds of formula I in which R, $R^1$, $R^2$ and $R^3$ are defined as in the first instance may be obtained, we have found that the following sequences of steps constitute preferred procedures.

Preferred Process (1). A 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one of the formula II in which R is as defined in the first instance (these substituents must be present at this stage if they are to be present in the final product of formula I) is reacted with a Grignard reagent prepared from methoxymethyl chloride to

yield the corresponding 5-methoxymethyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ol (VI, A = $OCH_3$) which is in turn treated with formic acid to yield the corresponding 10,11-dihydro-5H-dibenzo[a,d]cyclo-hepten-5-aldehyde (VII, $R^3$ = H). If it is desired to prepare compounds of formula I in which $R^3$ is methyl, the 5-ketone of formula II is reacted with a Grignard reagent prepared from an ethyl halide to yield the corresponding 5-ethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol (VI, A = $CH_3$), and said last-named compound is treated first with a dehydrating agent to yield the corresponding 5-ethylidene derivative (VII(a), $R^3$ = $CH_3$), then with an organic peracid to yield the corresponding 5-hydroxy-5-hydroxy-ethyl derivative (VII(b), $R^3$ = $CH_3$), and finally with a mineral acid to yield the corresponding 5-acetyl-10,11-dihydro-5H-dibenzo-[a,d]cycloheptene (VII, $R^3$ = $CH_3$).

Either the 5-aldehyde or the 5-acetyl derivative of formula VII is transformed to its corresponding oxime (VIII, $R^3$ = H or $CH_3$) which is in turn treated with a reducing agent, to yield the corresponding amine of formula IX, viz. (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (IX, $R^1$ = $R^3$ = H) or 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (IX, $R^1$ = H, $R^3$ = $CH_3$). Either one of said last-named compounds is then treated with a formylating agent, preferably formic acetic anhydride, to yield the corresponding N-formyl derivatives of formula XXVII(a), viz., N-formyl-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylamine (XXVII(a), $R^1$ = $R^3$ = H, Y = CHO) or N-formyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine

(XXVII(a), $R^1$ = H, $R^3$ = $CH_3$, Y = CHO), respectively, and the comp unds of formula XXVII(a) are treated with polyphosphoric acid to yield the corresponding Schiff base of formula XXVIII, viz., 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline (XXVIII, $R^2$ = $R^3$ = H) and 1-methyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (XXVIII, $R^2$ = H, $R^3$ = $CH_3$), respectively. Those compounds are converted to the corresponding compounds of formula I by one of the following four routes (a), (b), (c), or (d).

(a) When it is desired to obtain compounds of formula I in which $R^1$ and $R^2$ are both hydrogen and $R^3$ is as defined in the first instance, a Schiff base of formula XXVIII is treated with a reducing agent, preferably sodium borohydride, to yield the corresponding compounds of formula I, viz., 1,2,3,7,8,12b-hexahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinoline and 1-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, respectively.

(b) When it is desired to prepare compounds of formula I in which $R^1$ is an alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, or phenylalkyl group, $R^2$ is hydrogen, and $R^3$ is as defined in the first instance, it is preferred to treat said Schiff base of formula XXVIII with an alkylating agent of the formula $R^1Z$ in which $R^1$ is as defined immediately above and Z is a leaving group capable of bearing a pair of electrons, to obtain the corresponding quaternary Schiff base of formula XXIX. For example, when using ethyl iodide as the alkylating agent there are obtained 2-ethyl-1,7,8,12b-hexahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinolinium iodide and 1-methyl-2-ethyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolinium iodide. Said last-named quaternary Schiff bases of formula XXIX

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are th n treated with a reducing agent, preferably sodium boro-hydrid , to yi ld the corresponding comp unds of formula I, in which $R^1$ is as defined immediately above, $R^2$ is hydrogen, and $R^3$ is as defined in the first instance, for example, 2-ethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline (I, $R^1 = C_2H_5$, $R^2 = R^3 = H$) and 1-methyl-2-ethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline (I, $R^1 = C_2H_5$, $R^2 = H$, $R^3 = CH_3$) respectively.

(c) When it is desired to obtain compounds of formula I in which $R^1$ is hydrogen, $R^3$ is as defined in the first instance and $R^2$ is alkyl, alkenyl, (lower alkoxy)alkyl, cycloalkyl, cycloalkylalkyl, phenyl, or phenylalkyl, a Schiff base of formula XXVIII is treated with a Grignard reagent of the formula $R^2MgX$ in which $R^2$ is as defined immediately above and X is a halogen with an atomic weight greater than 19, to yield the corresponding compound of formula I. In this manner, when using Grignard reagents as defined above in which $R^2$ is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, amyl, isoamyl, hexyl, heptyl, octyl, nonyl, decyl, allyl, methoxymethyl, cyclopropyl, cyclohexylmethyl, phenyl, or benzyl, there are obtained the corresponding 3-methyl, 3-ethyl, 3-propyl, 3-isopropyl, 3-butyl, 3-isobutyl, 3-amyl, 3-isoamyl, 3-hexyl, 3-heptyl, 3-octyl, 3-decyl, 3-allyl, 3-methoxymethyl, 3-cyclopropyl, 3-cyclohexylmethyl, 3-phenyl, and 3-benzyl derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinoline (I, $R^1 = R^3 = H$, $R^2$ as defined immediately above) and of 1-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinoline (I, $R^1 = H$, $R^2$ as defined immediately above, $R^3 = CH_3$).

(d) When it is desired to obtain compounds of formula I in which $R^3$ is as defined in the first instance and both $R^1$ and $R^2$ are other than hydrogen as defined in the first instance, a quaternary Schiff base of formula XXIX obtained as described above under (b) is treated with a Grignard reagent of the formula $R^2MgX$ as defined above under (c). For example , when using the same Grignard reagents as described above under (c) and the same quaternary Schiff bases as described above under (b) there are obtained 3-methyl, 3-ethyl, 3-propyl, 3-isopropyl, 3-butyl, 3-isobutyl, 3-amyl, 3-isoamyl, 3-hexyl, 3-heptyl, 3-octyl, 3-decyl, 3-allyl, 3-methoxymethyl, 3-cyclopropyl, 3-cyclohexylmethyl, 3-phenyl, and 3-benzyl derivatives of 2-ethyl- or 1-methyl-2-ethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, respectively.

Preferred Process (2). A 5-ketone of formula II in which R is as defined in the first instance (if it is desired to obtain compounds of formula I in which R is other than hydrogen as defined in the first instance these substituents must be present in the 5-ketone of formula II) is treated with a Wittig reagent of the formula (lower alkyl-O)$_2$P(→O)CHR$^3$COO(lower alkyl) in which $R^3$ is hydrogen or methyl, for example trimethylphosphonoacetate or methyl-2-(dimethylphosphono)propionate, to yield the corresponding ylideneacetic or ylidenepropionic acid esters of formula XIII ($R^3$ = H or $CH_3$, M = COO(lower alkyl)) viz. (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene)acetic acid methyl ester (XIII, $R^3$ = H, M = $COOCH_3$) and 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propionic acid methyl ester (XIII, $R^3$ = $CH_3$, M = $COOCH_3$).

Said last-named ylideneacetic or yliden propionic acid esters are treated with an alkali metal hydroxide to yield the corresponding (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)acetic acid (XI, $R^3$ = H) or 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propionic acid (XI, $R^3$ = $CH_3$).

Said last-named acids of formula XI are treated with a reducing agent to yield the corresponding saturated acids of formula XV, viz. (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)acetic acid (XV, $R^3$ = H) and 2-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)propionic acid (XV, $R^3$ = $CH_3$), respectively, and said acids are converted to their respective acid halides, preferably the acid chlorides, by means of a halogenating agent such as, for example, thionyl chloride. Said last-named acid halides may be converted to the corresponding amines of formula IX by either one of three routes (a) or (b) or (c) described below.

(a) The acid halide is reacted with an alkali metal azide, preferably sodium azide, to yield the corresponding acid azide, which is heated to yield the corresponding isocyanate (XXIV, $R^3$ = H or $CH_3$) which, upon treatment with a mineral acid, yields the corresponding amine of formula IX ($R^1$ = H, $R^3$ = H or $CH_3$).

(b) The acid halide is treated with methanol to yield the corresponding methyl ester which is in turn treated with hydrazine hydrate to yield the corresponding acid hydrazide. Treatment of the latter with an alkali metal nitrite in acid solution yields the corresponding acid azide which is heated to yield the corresponding isocyanate (XXIV, $R^3$ = H or $CH_3$) from which the corresponding

amine of formula IX ($R^1$ = H, $R^3$ = H or $CH_3$) is obtained as described above.

(c) The acid halide is treated with ammonia to yield the corresponding amide of formula XVI, viz. (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide (XVI, $R^3$ = H) and 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionamide (XVI, $R^3$ = $CH_3$), respectively. Said last-named compounds are treated with bromine in solution in alkali metal hydroxide, preferably sodium hydroxide, to yield the corresponding amines of formula IX ($R^1$ = H, $R^3$ = H or $CH_3$).

The further conversion of the amines of formula IX obtained in the manners described above to the corresponding compounds of formula I is carried out in the same manner as described in Preferred Process (1).

Preferred Process(3). The isocyanate of formula XXIV in which R and $R^3$ are as defined in the first instance, obtained as described earlier in this Application, is treated with formic acid to yield the corresponding N-formyl derivative of formula XXVII(a) in which R and $R^3$ are as defined above, Y is CHO, and $R^1$ is hydrogen. Said compound of formula XXVII(a) is treated with polyphosphoric acid to yield the corresponding Schiff base of formula XXVIII in which R and $R^3$ are as defined in the first instance and $R^2$ is hydrogen. Said last-named Schiff base is treated with Raney nickel in the presence of a compound of the formula $R^1OH$ in which $R^1$ is alkyl, cycloalkyl, cycloalkylalkyl, or phenylalkyl, to yield the corresponding compound of formula I in which R and $R^3$ are as defined in the first instance, $R^2$ is hydrogen, and $R^1$ is as defined immediately above.

In any one of the abov procedures, both those described in the general part and those describ d in the secti ns entitled "Preferred Process s", when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one, the correspondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline (I, R = $R^1$ = $R^2$ = $R^3$ = H) and of its derivatives of formula I in which $R^1$, $R^2$ and $R^3$ have the significance other than hydrogen defined in the first instance are obtained.

Any of the compounds of formula I in which R, $R^1$, $R^2$ and $R^3$ are as defined in the first instance may be treated with a pharmaceutically acceptable acid to obtain the corresponding pharmaceutically acceptable acid addition salt thereof.

The following Examples will illustrate this invention.

EXAMPLE 1

5-Chloro-10,11-dihydro-5H-dibenz [a,d]cyclohepten may be prepared by the action of thionyl chloride in benzene on 5-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene,prepared by reduction of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one with sodium borohydride as described by Mychajlyszyn and Protiva in Coll. Czech. Chem. Commun., 24, 2955 (1959) or, more conveniently, by saturating a benzene solution of the carbinol with gaseous hydrogen chloride according to the procedure of van der Stelt, Harms and Nauta in J. Med. Pharm. Chem., 4, 335 (1961). The 5-cyano derivative is prepared as described in U.S. Patent 3,242,212, as follows.

To a stirred suspension of silver cyanide (56.5 g., 0.42 mole) in anhydrous acetonitrile (350 ml) is added the above 5-chloro compound (70.0 ., 0.31 mole), and the mixture is heated under reflux for twelve hours. The insoluble material is then separated from the warm mixture by filtration, and is washed with fresh acetonitrile. Removal of the solvent from the combined filtrates is done in vacuo and the residue thus obtained is recrystallized from ether-hexane or carbon tetrachloride-hexane mixture to yield 5-cyano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, m.p. 92-93°C.

When using as starting material the substituted 5-ketones of formula II in which R has the significance other than hydrogen defined in the first instance described earlier in this Application, the following substituted 5-cyano-10,11-dihydro-5H-dibenzo[a,d]-cycloheptenes are obtained: 1,2,3 and 4-methyl, 1,4-dimethyl,

3-t-butyl, 1,2, and 3-chloro, 3-bromo, 3-fluoro, 2,7-dibromo, 2- and 3-hydroxy, 2- and 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl,3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro and 3,9-dinitro. 3-Chloro-5-cyano-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene, m.p. 133-134°C is described in Canadian Patent 331,522.

EXAMPLE 2

A solution of chloromethyl methyl ether (40.2 g, 0.5 mole, freshly distilled) in dry tetrahydrofuran (80 ml) is prepared and 5 ml thereof is added to a stirred mixture of magnesium turnings (12.0 g, 0.5 g - atom) and mercuric chloride (500 mg) in tetrahydrofuran (20 ml); an exothermic reaction ensues. The flask is cooled to 0° ± 10° and the remainder of the above solution is added dropwise with thorough agitation. After completion of addition a solution of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (56.1 g 0.25 mole) in tetrahydrofuran (80 ml) is added dropwise. The reaction mixture is stirred overnight at room temperature and the complex is hydrolyzed with iced ammonium chloride solution. The aqueous layer is extracted with ether (3 x 100 ml) and the combined extracts are washed with sodium chloride solution, dried and evaporated in vacuo to yield 5-methoxymethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol as an oil, $\nu_{max}^{film}$ : 3500, 2820 $cm^{-1}$, b.p. 143-4°/0.05 mm:

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one

the corr spondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethyl-aminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 5-methoxymethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol are obtained.

EXAMPLE 3

A solution of 5-methoxymethyl-10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-ol (52.0 g, 0.21 mole) and formic acid (60 ml) is heated under reflux for 3 hours; cooled, diluted with water (500 ml), and the oil extracted into benzene. Evaporation of the solvent yields the crude aldehyde as a viscous oil, which is stirred overnight at room temperature with a solution of "Girard-T" reagent (40 g) in methanol (400 ml). The precipitate is combined with the residue obtained on evaporation of the methanol. The Girard adduct is dissolved in water and the solution is extracted with ether (6 x 100 ml) to remove non-carbonylic impurities. Hydrolysis of the adduct is effected by stirring the aqueous solution overnight at 25°C with 40% sulfuric acid. The precipitated product is filtered off, washed well with water and dried to yield 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-aldehyde, m.p. 78°C, after crystallization from hexane, $\nu_{max}^{film}$ : 2680, 2790, 2825, 1715 cm-1, also characterized as the 2,4-dinitrophenylhydrazone derivative: m.p. 217° (acetic acid).

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 5-methoxymethyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol

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th c rrespondingly substituted 1-, 2-, 3-, r 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethyl-aminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-aldehyde are obtained.

EXAMPLE 4

(a) A Grignard reagent is pr pared from ethyl bromide (109 g, 1.0 mole) and added with stirring to a refluxing solution of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (II, R = H, 101 g) in diethyl ether (300 ml). The mixture is refluxed for two hours, cooled, and decomposed by addition of water and acetic acid. The ether layer is separated, washed with water, dried with anhydrous sodium sulfate, and evaporated, to yield 5-ethyl-5-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (VI, R = H, H = $CH_3$), $\gamma^{CHCl_3}_{max}$ 3610 $cm^{-1}$.

(b) Said last-named compound is heated at 50-60°C for 15 minutes with a 1:1 mixture of acetic anhydride and acetyl chloride (150 ml), the mixture poured into ice-water, allowed to stand at room temperature for 12 hours, and extracted with ether. The ether extracts are washed, dried with anhydrous sodium sulfate, evaporated, and the residue distilled under reduced pressure, to yield 5-ethylidene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (VIIa, R = H, $R^3$ = $CH_3$), b.p. 162°C/2.5 mm Hg.

(c) The 5-ethylidene derivative obtained as described above is dissolved in anhydrous formic acid (425 ml), at 55-65°C and hydrogen peroxide (36%, 60 ml) is added. The mixture is kept at 65-75°C for 2.5 hours, cooled, extracted with ether, the ether extracts washed with water and 10% sodium hydroxide, dried with sodium sulfate, and evaporated to yield 5-hydroxy-5-hydroxyethyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (VII b, R = H, $R^3$ = $CH_3$), $\gamma^{CHCl_3}_{max}$ 3600 $cm^{-1}$.

(d) Said last-named compound is reflux d for 2.5 hours with sulfuric acid (25% vol/vol, 200 ml), the mixture is cooled, extracted with ether, the ether extracts washed with water, dried with sodium sulfate, evaporated, and the residue is crystallized from hexane, to yield 5-acetyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (VII, R = H, $R^3 = CH_3$), m.p. 70-72°C. The same compound has also been described in German Patent 1,298,523.

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one

the correspondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 5-acetyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene are obtained.

EXAMPLE 5

(a) Powdered sodium hydroxide (6.0 g, 0.15 mole) is added in portions to a suspension of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-aldehyde (6.66 g, 0.03 mole) and hydroxylamine hydrochloride (4.16 g, 0.06 mole) in ethanol (50 ml) and water (15 ml). The mixture is kept at room temperature for 2 hours, poured into water (300 ml) and the precipitate is collected and dried to give 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-aldoxime (VIII, $R = R^3 = H$) with m.p. 167-168.5°C after two recrystallizations from ethanol.

In a similar manner, 5-acetyl-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene (6.5 g), hydroxylamine hydrochloride (4.0 g), and pyridine (100 ml) are refluxed for 16 hours, the pyridine is removed under reduced pressure and the residue is distributed between water and chloroform. The chloroform extracts are dried with sodium sulfate and evaporated to yield methyl-(10,11-dihydro-5H-dibenzo[a,d]-cycloheptene-5-yl)-ketoxime, $\nu_{max}^{CHCl_3}$ 3580, 3320 $cm^{-1}$.

(b) Raney alloy (1.5 g) is added in one portion to a well-stirred mixture of the aldoxime obtained as described above(1.0g, 0.0043 mole) in ethanol (25 ml) and 2N sodium hydroxide (20 ml). The mixture is filtered after one hour, the filtrate evaporated under reduced pressure and diluted with water. The aqueous mixture is extracted with dichloromethane (2 x 25 ml). The dried organic layer is evaporated under reduced pressure to give (10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl)methylamine as an oil with b.p. 150-154°C/0.2-0.3 mm Hg, $n_D^{23}$ 1.6122, (IX, $R = R^1 = R^3 = H$). The oil is dissolved in ether and treated with ethereal hydrogen chloride to give the hydrochloride salt, m.p. ≥ 295°C, from which the above free amine is obtained by

treatment with sodium hydroxide, extraction with dichloromethane and evaporation of the solvent.

In the same manner, when starting with methyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ketoxime obtained as described above, there is obtained 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (IX, R = $R^1$ = H, $R^3$ = $CH_3$) as an oil, $\gamma_{max}^{CHCl_3}$ 3358, 3275 $cm^{-1}$.

(c)The aldoxime described above (70.0 g) is dissolved in a mixture of ethanol (260 ml) and benzene (30 ml) containing sodium hydroxide (40 g). Commercial Raney nickel (20 g), activated with a little acetic acid, is added, and the mixture is stirred at room temperature (28°C) under hydrogen at 6 p.s.i. for 48 hours. Filtration, evaporation of the solvent, dilution with water, extraction with dichloromethane, and evaporation of the latter yields (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, identical with the compound obtained as described under (b). Alternatively, the mixture obtained after hydrogenation is filtered evaporated, the residue taken up in isopropanol and hydrochloric acid is added, thus precipitating the hydrochloride salt of the amine, identical with the compound described above under (b).

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-

7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-aldehyde r 5-acetyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, the correspondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine and of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine are obtained. The hydrochloride salt of 3-chloro-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine has m.p. 300-310°C (IX, R = 3-Cl, $R^1 = R^3 = H$, see also Example 14).

EXAMPLE 6

(a) 10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-aldoxime (2.37 g, 0.01 mole) and acetic anhydride (10 ml) are refluxed for three hours. The cooled mixture is poured onto ice-water, the precipitate is collected and dried to yield 5-cyano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene identical with the same compound as described in Example 1.

(b) Raney alloy (9.7 g) is added in two portions to a mixture of 5-cyano-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (6.57 g, 0.03 mole) in ethanol (250 ml) and 2N sodium hydroxide (125 ml). After one hour the mixture is filtered and the ethanol removed under reduced pressure. The residue is diluted with water, extracted with benzene and washed with 1N hydrochloric acid to give the hydrochloride salt m.p. >295°.

The salt is converted to the free base with dilute sodium hydroxide solution to give 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine identical with the same compound as described in Example 5.

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-aldoxime,

the correspondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine are obtained.

EXAMPLE 7

10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-aldehyde (2.2 g, 0.01 mole) is dissolved in ethanol (15 ml) and the solution is saturated with gaseous ammonia. It is hydrogenated over Raney nickel (50 mg) for 1 hour at 70°C and 1300 p.s.i.; the temperature is then raised to 100°Cand maintained there for one additional hour. The catalyst is filtered off and the solvent evaporated. The residue is dissolved in ether and treated with ethereal hydrogen chloride to give the hydrochloride salt with m.p. >285°, which is converted to the free base by treatment with dilute sodium hydroxide solution, to yield (10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-yl)-methylamine, identical with the same compound as described in Example 5.

10,11-Dihydro-5H-dibenzo[a,d]cycloheptene-5-aldehyde (10.0 g) is dissolved in ethanol (100 ml) containing ethylamine (5.0 g). The mixture is treated with hydrogen in the presence of Raney nickel (2.0 g) for 1 hour at 70°C and 1300 p.s.i. The mixture is filtered and the filtrate evaporated to give N-ethyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine as an oil, λ max 270 mμ (ε 714).

In the same manner, by using methylamine, allylamine, cyclopentylamine, cyclohexylmethylamine, or benzylamine, the corresponding N-methyl-, N-allyl-, N-cyclopentyl-, N-cyclohexylmethyl-, and N-benzyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamines are obtained.

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In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, r 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-aldehyde,

the correspondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine and of their N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, and N-benzyl derivatives are obtained.

EXAMPLE 8

(a) 10,11-Dihydro-5H-dib nzo[a,d]cyclohepten-5-one (25.0 g), methyl bromoacetate (22.0 g) and freshly activated zinc (14.3 g) are reacted together by refluxing in anhydrous ether (300 ml) for 6 hours. The mixture is poured onto crushed ice, acidified with hydrochloric acid and the ether layer separated, washed with sodium bicarbonate solution, dried with sodium sulfate and evaporated to give 5-hydroxy-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl) acetic acid methyl ester (X, R = $R^3$ = H, lower alkyl = $CH_3$) $\nu_{max}^{CHCl_3}$ 3600, 1720 $cm^{-1}$. The corresponding isopropyl and t-butyl esters are obtained in the same manner from isopropyl or t-butyl bromoacetate.

In the same manner, by using methyl, isopropyl or t-butyl α-bromopropionate, 5-hydroxy-2-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)propionic acid methyl, isopropyl, and t-butyl ester are obtained.

(b) Magnesium (14.6 gm., 0.6 mole) is added to a 1 liter, 3-neck flask equipped with a stirrer, condenser and dropping funnel. Ethyl bromide (66.0 gm., 0.6 mole) dissolved in ether (250 ml) is added slowly and the resulting exothermic reaction controlled by cooling with an ice bath. The mixture is refluxed for 1 hour, cooled to 0°C, diethylamine (43.8 gm., 0.6 mole) dissolved in 75 ml. of ether is added over 30 minutes and the mixture is refluxed 30 minutes. The mixture is cooled to -5° and 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (62.5 gm., 0.3 mole) and t-butyl acetate (34.8 gm., 0.3 mole) combined together in 200 ml of ether are added over a 30 minute period. The mixture

is then brought to reflux temperature and held there for 2 hours, cooled and poured onto an ice-water mixture containing 50 gm. of ammonium chloride. Benzene is added , the mixture is filtered through celite and the organic phase separated and washed with water and dried. Evaporation of the solvent and crystallization of the residue from aqueous isopropanol yields 5-hydroxy-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)acetic acid t-butyl ester as colourless crystals with m.p. 100-103°C. (X = R = $R^3$ = H, lower alkyl = t-butyl).

In the same manner, by using magnesium (9.8 gm., 0.4 mole), ethyl bromide (43.5 gm., 0.4 mole) diethylamine (29.4 gm., 0.4 mole), isopropyl acetate (20.4 gm., 0.2 mole) and 10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-one (41.6 gm., 0.2 mole) there is obtained 5-hydroxy-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)acetic acid isopropyl ester, m.p. 102-104°C (X, R = $R^3$ = H, lower alkyl = isopropyl).

(c) 5-Hydroxy-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)acetic acid t-butyl ester (175 gm.) is dissolved in a mixture of 875 ml. of glacial acetic acid and 875 ml. of chloroform. The mixture is cooled to 10° and, with stirring, anhydrous hydrogen bromide is bubbled into the solution for 20 minutes not allowing the temperature to exceed 15°C. The reaction mixture is poured into 1700 ml. of water, the chloroform phase is separated and the aqueous phase extracted once, with 2.0 litres of chloroform. The combined chloroform phases are extracted with successive 1 liter portions of 10% aqueous sodium hydroxide, the alkaline

xtracts acidif d the solution extracted with 2000 and 2 x 1000 ml of chloroform.The chloroform extract is back-washed with 1 liter of water, dried with sodium sulfate, treated with charcoal, evaporated to dryness and the solid crystallized from a 1:1 mixture of methanol and benzene. Cooling at 0°C yields (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)acetic acid (XI, R = $R^3$ = H) with m.p. 169.5 -170.5°C.

The same compound is also obtained when (5-hydroxy)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)acetic acid isopropyl ester (5.0 gm) is dissolved in a mixture of 25 ml of chloroform and 25 ml of acetic acid and treated at 10°C for two hours with anhydrous hydrogen bromide, then allowed to remain at 22° overnight. The dark brown solution is poured into 50 ml of water and the mixture worked up as described above.

(d) 10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-one (2.0 g) is heated for 6 hours in tetrahydrofuran (50 ml) with sodio diethyl malonate prepared from diethyl malonate (1.6 g) and sodium (230 mg). The solvent is removed under reduced pressure and the residual (10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-ylidene)malonic acid diethyl ester is heated with 5N sodium hydroxide (50 ml) and ethanol (50 ml) for 2 hours on the steam bath. The ethanol is removed under reduced pressure the aqueous solution is acidifed with concentrated hydrochloric acid and extracted with chloroform. The chloroform solution is dried with sodium sulfate, evaporated, and the residue is heated under reduced pressure at 100° for 3 hours to give (10,11-dihydro-

5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid, identical with the same compound obtained as described above.

(e) Trimethylphosphonoacetate (218.9 g, 1.2 moles) is added slowly to a suspension of 50% sodium hydride (56 g., 1.2 moles) in 500 ml of dry dimethylformamide at 65 to 70°C with stirring. A solution of 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-one (100 g., 0.48 mole) in 300 ml of dry dimethyl formamide is added and the mixture is heated to 90°C for 7 hours. It is then poured into cold water and extracted with 2 x 250 ml benzene. The benzene extracts are combined, washed with water, dried over anhydrous sodium sulfate, filtered through celite and evaporated to dryness. The crude product obtained is crystallized from a mixture of isopropanol and water to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid methyl ester (XIII, $R = R^3 = H$, $M = COOCH_3$), m.p. 70-72°C, $\lambda_{max}^{CHCl_3}$ 1612, 1220 $cm^{-1}$, $\lambda_{max}^{EtOH}$ 264 mμ (ε 12200)

A mixture of said last-named compound (6.1 g.), 25 ml of ethanol, 25 ml of water and sodium hydroxide (3 g) is refluxed for 2 hours. The ethanol is removed by distillation and the aqueous solution obtained is washed with 50 ml of toluene and acidified with 10% hydrochloric acid. The product precipitated is collected by filtration, washed with water and dried, to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid (XI, $R = R^3 = H$), identical with the compound obtained as described above.

In the same manner, when using methyl 2-(dimethylphosphono)-propionate there are obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclo-

hepten-5-ylidene)-propionic acid (XI, R = H, $R^3 = CH_3$) and its methyl ester (XIII, R = H, $R^3 = CH_3$, M = $COOCH_3$).

(f) Dimethylphosphonoacetonitrile (179 g) is added to a suspension of 50% sodium hydride (56 g) in 500 ml dimethylformamide at 65-70°C with stirring, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (100 g dissolved in 300 ml dimethylformamide) is added and the mixture is heated to 90-95°C for 10 hours. Quenching with water, extraction with benzene (3 x 300 ml), washing with water, drying over anhydrous sodium sulfate, and evaporation of the benzene yields (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetonitrile, (XIII, R = $R^3$ = H, M = CN), $\nu_{max}^{CHCl_3}$ 2180 $cm^{-1}$.

Said last-named compound (17.0 g) is dissolved in isopropanol (50 ml) and refluxed for 22 hours with 50 ml of a 50% solution of potassium hydroxide in aqueous methanol. Cooling, evaporation of solvent, addition of water, acidification with hydrochloric acid, filtration and crystallization from isopropanol yields (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid, identical with the same compound obtained as descrbied above.

In the same manner, by using 2-(dimethylphosphono)propionitrile and proceeding as above, 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionitrile and 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionic acid are obtained.

In the same manner, when using as starting material th 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one,

the correspondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 5-hydroxy-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)acetic acid and 5-hydroxy-2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)propionic acid methyl, isopropyl, and t-butyl esters, of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene acetic acid and 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionic acid, and of the methyl esters and nitriles of said last-named compounds are obtained.

EXAMPLE 9

(a) (10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetonitrile (1.0 g) is suspended in a mixture of sulphuric acid (1 ml),acetic acid (1 ml), and water (1 ml) and refluxed with stirring for one hour. The mixture is cooled, diluted with water, extracted with chloroform, the chloroform washed with 5% aqueous sodium hydroxide, dried and evaporated to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetamide (XIV, R = $R^3$ = H), m.p. 166-167°C.

In the same manner, when using 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionitrile and proceeding as above, the corresponding 2-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene)-propionamide (XIV, R = H, $R^3$ = $CH_3$) is obtained.

(b) (10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)acetonitrile (17.5 g) is dissolved in isopropanol (50 ml) and a solution of potassium hydroxide (5.3 g) in isopropanol (40 ml) is added. The mixture is refluxed for 10 hours, the solvent evaporated under reduced pressure, methylene dichloride (100 ml) is added with stirring, and washed with water, dried, and evaporated, to yield 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetamide, identical with the compound obtained as described above.

In the same manner, when using 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionitrile as the starting material, 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionamide is obtained.

(c) Diethylphosphonoac tamid (23.4 g) is added slowly to a suspension of 50% sodium hydride (5.8 g) in 50 ml of dry dimethylformamide at 65 to 70°C with stirring. A solution of 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-one (10.0 g) in 30 ml of dry dimethyl formamide is added andthe mixture is heated to 90°C for 7 hours. It is then poured into cold water, neutralized with acetic acid, and extracted with 2 x 100 ml benzene. The benzene extracts are combined, washed with water, dried over anhydrous sodium sulfate, filtered through celite and evaporated to dryness. The crude product obtained is crystallized from a mixture of isopropanol and water to yield (10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-ylidene)-acetamide (XIV, R = $R^3$ = H) m.p. 166-167°C, identical with the same compound obtained as described above.

In the same manner, but using an equivalent amount of 2-(diethylphosphono)-propionamide and proceeding as above, there is obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionamide (XIV, R = H, $R^3$ = $CH_3$).

(d) (10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetamide obtained as described above (4.9 g) is dissolved in anhydrous ethanol (50 ml), palladium on charcoal (10%, 1.2 g) is added and the mixture is shaken with hydrogen at 6 p.s.i. at room temperature for 10 hours. The mixture is warmed to 60°C, filtered, evaporated, and the residue is crystallized from isopropanol to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide (XVI, R = $R^3$ = H), m.p. 136-138°C, $\nu_{max}^{CHCl_3}$ 3530, 3500, 3340, 3190,

1678 $cm^{-1}$, NMR($CDCl_3$) 2.90, 3.16, 4.66, 5.44, 7.08 p.p.m.

In the same manner, when using 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionamide and proceeding as above there is obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionamide (XVI, R = H, $R^3 = CH_3$).

(e) (10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid (29.0 gm) is dissolved in 125 ml. of anhydrous ethanol and 2.0 gm of 10% palladium on charcoal is added. The mixture is hydrogenated at 40°C and 50 p.s.i. The theoretical uptake is observed in 9 hours. After the end of the hydrogenation, the mixture is allowed to stand at 22° overnight. Benzene (150 ml) and anhydrous ethanol (150 ml) are added, the catalyst is removed by filtration, the filtrate evaporated and the residue crystallized from benzene, to yield 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid (XV, R = $R^3$ = H), m.p. 163-164°C, $\lambda_{max}^{EtOH}$ 266 mμ (ε 620).

In the same manner, when using 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionic acid, there is obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid (XV, R = H, $R^3 = CH_3$).

(f) A mixture of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid (10 g) and 20 ml of thionyl chloride is refluxed for 30 minutes. The excess thionyl chloride is removed by distillation under reduced pressure and the residue obtained is dissolved in 150 ml of toluene. The resulting toluene solution is saturated with ammonia at room temperature with stirring and the precipitate is filtered, washed with

t luene and water, and dri d to yi ld (10,11-dihydro-5H-dib nzo-[a,d] ycloheptene-5-yl)acetamid (XVI, R = $R^3$ = H), id ntical with the same compound obtained as described above. In the same manner, when using 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid and proceeding as above, there is obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionamide.

(g) In a similar manner, a mixture of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)acetic acid (8.4 g) and thionyl chloride (17 ml) is refluxed for 30 minutes. Excess thionyl chloride is removed under reduced pressure, the residue is dissolved in 120 ml of toluene and saturated with gaseous ammonia at room temperature with stirring. Filtration, washing with toluene, and drying yields (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidene)-acetamide (XIV, R = $R^3$ = H), identical with the product described in Example 9(c).

Said last-named compound (5.2 g) is dissolved in anhydrous ethanol (50 ml), palladium on charcoal (10%, 1.5 g) is added, the mixture is shaken with hydrogen at 5.5 p.s.i. at room temperature for 16 hours, warmed to 60°C, filtered, the catalyst washed with ethanol, and the filtrate evaporated to yield, after crystallization from isopropanol, (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide (XVI, R = $R^3$ = H), identical with the compound described in Example 9(d).

In the same manner, when starting with 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionic acid, and proceeding as above, there is obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclo-hepten-5-yl)-propionamide.

(h) A solution of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid methyl ester (14.2 g) in 250 ml of methanol containing 0.1 g sodium metal is saturated with ammonia at 10°C and refluxed for 48 hours using a condenser cooled with solid carbon dioxide in acetone. The mixture is quenched with ice water (500 ml), filtered, the precipitate washed with water and dried, to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetamide (XIV, $R=R^3=H$), identical with the compound obtained as described in Example 9(a).

Said last-named compound (10.5 g) is dissolved in anhydrous ethanol (100 ml), palladium on charcoal (10%, 2.5 g) is added, the mixture is shaken with hydrogen at 6 p.s.i. at room temperature for 14 hours, filtered, the catalyst washed with ethanol, and the filtrate evaporated to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide (XVI, $R=R^3=H$), identical with the compound obtained as described in Example 9(d).

In the same manner, when using as starting material 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionic acid methyl ester and proceeding as above, 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionamide (XVI, $R=H$, $R^3=CH_3$) is obtained.

(i) A solution of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid methyl ester (13.2 g) in methanol (100 ml) is shaken with hydrogen at 8 p.s.i. and 25°C with palladium on charcoal (10%, 3.0 g) for 2 days, filtered, the catalyst washed with methanol, and the filtrate evaporated to

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yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid methyl ester (XVII, $R = R^3 = H$, lower alkyl = $CH_3$) as a colourless liquid, $\nu_{max}^{CHCl_3}$ 1740 $cm^{-1}$, NMR ($CDCl_3$) 3.05, 3.18, 3.56, 4.72, 7.12 p.p.m.

A solution of said last-named compound (15.0 g) in methanol (250 ml) containing 0.1 g of sodium metal is saturated with ammonia at 10°C and refluxed for 2 days using a condenser cooled with dry ice and acetone. The mixture is poured into cold water (500 ml) with stirring, filtered, the precipitate washed with water and dried, to yield (10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)-acetamide (XVI, $R = R^3 = H$) identical with the compound described in Example 9(d).

In the same manner, when using 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionic acid methyl ester as starting material and proceeding as above, 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionamide (XVI, R= H, $R^3 = CH_3$) is obtained.

(j) A mixture f (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid methyl ester (6.2 g), ethanol (25 ml), water (25 ml) and sodium hydroxide is refluxed for 2 hours, the ethanol substantially removed by distillation, the residual solution washed with toluene (50 ml) and acidified with 10% hydrochloric acid, to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid (XV, R = $R^3$ = H), identical with the compound obtained as described in Example 9(e). In the same manner, when using as starting material 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid methyl ester and proceeding as above, 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid (XV, R = H, $R^3$ = $CH_3$) is obtained.

Alternatively, when using as starting materials the corresponding isopropyl or t-butyl esters of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid (5.2 g) and treating them in solution in a mixture of 25 ml of chloroform and 25 ml of acetic acid at 5-15°C with anhydrous hydrogen bromide for 2 hours, quenching with ice water, separating, extracting the aqueous phase with chloroform, extracting the combined chloroform extracts with 10% aqueous sodium hydroxide, and acidifying the alkaline extracts, there is obtained (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid, identical with the compound described in Example 9(e). In the same manner, when using as starting materials the isopropyl or t-butyl esters of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid and proceeding as above, there is obtained

2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid. (10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid or 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid are treated first with thionyl chloride and then with ammonia in the manner described in Example 9(f) to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide (XVI, R = $R^3$ = H) or 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)propionamide (XVI, R = H, $R^3$ = $CH_3$), respectively.

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one, of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid or 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionic acid, or of their respective nitriles or methyl, isopropyl, or t-butyl esters, the correspondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide or of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionamide are respectively obtained.

EXAMPLE 10

(a) A mixture of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol (III, 40.5 g), cyanoacetic acid (23.5 g, or 30.5 g ethyl cyanoacetate), and anhydrous zinc chloride (9.5 g) in glacial acetic acid (50 ml) is refluxed with stirring for 8 hours, cooled, poured into ice water (500 ml) and respectively extracted with ether. The combined ether extracts are rapidly washed with 10% aqueous sodium hydroxide solution, dried with anhydrous magnesium sulfate, and evaporated, to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetonitrile (XVIII, R = $R^3$ = H), $\nu_{max}^{CHCl_3}$ 2210 $cm^{-1}$.

(b) (10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetonitrile (5.5 g) is suspended in a mixture of sulfuric acid (5.5 ml), acetic acid (5.5 ml) and water (5.5 ml) and refluxed with stirring for one hour. The mixture is cooled, diluted with water, extracted with chloroform, the chloroform washed with 5% aqueous sodium hydroxide, dried and evaporated to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide (XVI, R = $R^3$ = H), identical with the compound obtained as described in Example 9(d).

Alternatively, the same compound is also obtained when refluxing the above acetonitrile (1.0 g) with 57% aqueous sulfuric acid (5 ml) for 2 hours and working up as above, or when refluxing the above acetonitrile (9.0 g) in isopropanol (25 ml) with a solution of potassium hydroxide (2.7 g) in isopropanol (20 ml) for 10 hours, evaporating the isopropanol under reduced pressure, extracting with methylene dichloride and evaporating the solvent.

(c) The (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetonitrile obtained in Example 10(a) is refluxed for 20 hours in a mixture of potassium hydroxide (19.5 g), ethanol (40 ml) and water (10 ml), the ethanol is substantially evaporated, the residual solution cooled, water is added, and the mixture is extracted with ether. The alkaline aqueous phase is acidified with 10% hydrochloric acid and filtered, to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid (XV, R = $R^3$ = H), identical with the compound obtained as described in Example 9(e). The same compound is also obtained when refluxing the above acetonitrile (5.0 g) with 25% sulfuric acid (80 ml) for 8 hours, pouring on ice, extracting with chloroform, extracting the chloroform with 10% aqueous sodium hydroxide, acidifying the aqueous extracts with 10% sulfuric acid, and filtering.

The acetic acid XV obtained as described above is converted to the corresponding amide XVI (R = $R^3$ = H) as described in Example 9(f). In the same manner, when starting with an equivalent amount of α-cyanopropionic acid or ethyl α-cyanopropionate and proceeding as in Examples 10(b) or 10(c) there are obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionitrile (XVIII, R = H, $R^3$ = $CH_3$), 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid (XV, R = H, $R^3$ = $CH_3$) and its corresponding amide XVI (R = H, $R^3$ = $CH_3$).

(d) A solution of (10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-ylidene)-acetonitrile (13.5 g) obtained as

described in 8(f) in thanol (100 ml) is agitated with hydrogen at 8 p.s.i. and at 25°C in the presence of 10% palladium on charcoal (3.0 g) for 2 days filtered, and the solvent evaporated to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetonitrile (XVIII, R = $R^3$ = H), identical with the compound described in Example 10(a). In the same manner, when starting with 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propionitrile and proceeding as above, 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionitrile is obtained.

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol the correspondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetonitrile and of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionitrile are obtained and converted to the corresponding -acetamides and -propionamides or -acetic acids -propionic acids, respectively.

EXAMPLE 11

(a) Liquid ammonia (120-150 ml) is condensed in a thoroughly dried flask equipped with a gas inlet tube, a dropping funnel, and a condenser. The inlet tube and the outlet of the condenser are protected by tubes filled with solid potassium hydroxide, and flask and condenser are cooled with solid carbon dioxide in acetone. Acetylene gas, throoughly washed with water to remove acetone and dried in an apparatus from which all air has previously been swept out by nitrogen, is bubbled through the liquid ammonia while sodium metal (13.8 g) is added in small portions at such a rate that the blue colour indicating excess sodium is discharged before each fresh portion is added (about 30 minutes). The addition of acetylene is reduced, and a solution of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (22.0 g) in about 200 ml of ether is added slowly over about 40 minutes. The addition of acetylene is stopped altogether, the mixture is allowed to stand at -60°C to -50°C for 5 hours, the cooling bath is removed and the ammonia is allowed to evaporate at room temperature over night. Water is added, the ether layer separated, washed with water, dried with anhydrous sodium sulfate, and evaporated. The residue is crystallized from petroleum ether (b.p. 40-60°C) to yield 10,11-dihydro-5-ethynyl-5H-dibenzo[a,d] cyclohepten-5-ol, with m.p. 72-73°C (XIX, R = H).

(b) Said last-named compound (6.0 g) is dissolved in ethanol (15 ml) and the solution is added over a period of about 30 minutes to a refluxing mixture of ethanol (30 ml), water (7 ml) and concentrated sulfuric acid (3.0 g). Refluxing is continued

for another 15 minutes, the mixture is cooled, poured on ice, filtered, and the solid crystallized from petroleum ether (b.p. 40-60°C) to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetaldehyde with m.p. 70-72°C (XX, R = H).

(c) Said last-named compound (5.3 g), dissolved in ethanol (55 ml) is mixed with a solution of silver nitrate (6.6 g) in water (6.6 ml), and the mixture is added dropwise with stirring at about 30°C to a solution of potassium hydroxide (5.4 g) in water (3.5 ml) and ethanol (52.5 ml). Stirring is continued until the temperature begins to drop, the mixture is filtered, the precipitate washed with ethanol and hot water, the combined filtrates are diluted with water, acidified with 10% nitric acid, and filtered, to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid (XI, R = $R^3$ = H), identical with the compound obtained as described by Example 8(c). Hydrogenation of said last-named compound as described in Example 9(e) followed by treatment with thionyl chloride and ammonia as described in Example 9(f) yields the corresponding acetamide XVI (R = $R^3$ = H).

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one

the c rrespondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5-ethynyl-5H-dibenzo[a,d]cyclohepten-5-ol, of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetaldehyde, of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-acetic acid, of (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-acetic acid, and of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide are respectively obtained.

EXAMPLE 12

(a) A mixture of magnesium metal (3.6 g), diethyl malonate (24.0 g) and anhydrous ethanol (30 ml) is brought to reflux and a few drops of carbon tetrachloride are added to start the reaction. Further heating is stopped and the mixture is stirred until all the magnesium has reacted. Ethanol is evaporated under reduced pressure, dioxan (15 ml) is added and evaporated under reduced pressure, and this operation is repeated until the ethanol has been removed as completely as possible. Anhydrous tetrahydrofuran (60 ml), and a solution of 5-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (34.3 g, obtained as described in Example 1) in anhydrous tetrahydrofuran (120 ml) are added, the mixture is refluxed for 4 hours, and the solvent is evaporated under reduced pressure. The residue is poured into water, acidified with 10% hydrochloric acid, extracted with ether, the ether extracts dried with anhydrous sodium sulfate, and evaporated, to yield 2-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-malonic acid diethyl ester (XXI, R = $R^3$ = H, Q = $C_2H_5$), $\gamma_{max}^{CHCl_3}$ 1710 $cm^{-1}$. In the same manner, when using diethyl 2-methylmalonate as one of the starting materials and proceeding as above, there is obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methylmalonic acid diethyl ester (XXI, R = H, $R^3$ = $CH_3$, Q = $C_2H_5$).

(b) The 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-malonic acid obtained as described in Example 12(a) is refluxed for 12 hours with a solution of potassium hydroxide (30.0 g) in ethanol (60 ml) and water (15 ml), the ethanol is

evaporated under reduced pressure, the residue is diluted with water, and extracted with ether. The alkaline aqueous phase is acidified with 10% hydrochloric acid, extracted with ether, the ether washed, dried with anhydrous sodium sulfate, and evaporated, to yield 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-malonic acid (XXI, R = $R^3$ = Q = H) with m.p. 184-185°C (dec.) after crystallization from ethyl acetate. In the same manner, when using as starting material 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methylmalonic acid diethyl ester and proceeding as above there is obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methylmalonic acid (XXI, R = Q = H, $R^3$ = $CH_3$).

(c) The 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-malonic acid obtained as described in Example 12(b) is heated at 165-172°C until evolution of carbon dioxide has ceased. The residue is crystallized from benzene to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid (XV, R = $R^3$ = H), identical with the compound obtained as described in Example 9(e). In the same manner 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methylmalonic acid yields 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid (XV, R = H, $R^3$ = $CH_3$). Said last-named compounds are converted to the corresponding amides of formula XVI by the method described in Example 9(f).

(d) A solution of (10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-ylidene)-malonic acid diethyl ester (5.8 g) obtained as

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described in Example 8(d), in ethanol (100 ml) is agitated with hydr gen in the presence of 10% palladium on charcoal (1.5 g) for 18 hours at room temperature and 8 p.s.i. The catalyst is filtered off, washed with ethanol, and the combined filtrates are evaporated, to yield 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-maloric acid diethyl ester (XXI, R = $R^3$ = H, Q = $C_2H_5$), identical with the compound obtained as described in Example 12(a). Conversion of said last-named compound to the corresponding malonic acid, -acetic acid, and -acetamide is carried out as described in Examples 12(b) and (c).

(e) To a suspension of 10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ol (24.0 g), obtained as described in Example 1, in glacial acetic acid (90 ml) there is added a solution of malonic acid (13.2 g) in glacial acetic acid (90 ml) and the mixture is stirred at 65-75°C for two hours. Some crystalline material separates after stirring for 16 hours at room temperature and is filtered off. The filtrate is poured into water (300 ml), the precipitate filtered, dissolved in 10% aqueous sodium hydroxide, filtered, acidified with 10% hydrochloric acid, filtered, and the precipitate dissolved in ether. The crystalline material obtained above is also added to this ether solution, which is washed with water, dried with anhydrous magnesium sulfate, and evaporated, to yield 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-malonic acid (XXI, R = $R^3$ = Q = H), identical with the compound obtained as described in Example 12(b). In the same manner, when using 2-methylmalonic acid as starting

material and proceeding as above there is obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methylmalonic acid (XXI, R = Q= H, $R^3$ = $CH_3$). Both the above compounds of formula XXI are converted to their corresponding -acetic acid and -propionic acid, and -acetamide and -propionamide by the method described in Examples 12(c) and 9(f).

Alternatively, the 2-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)malonic acid obtained as described above (15.8 g) is dissolved in pyridine (45 ml), heated on the steam bath for 2 hours, poured into 15% w/v hydrochloric acid, filtered, the precipitate dissolved in ether, the ether solution thoroughly washed with water, dried with anhydrous magnesium sulfate, and evaporated to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid (XV, R = $R^3$ = H), identical with the compound obtained as described in Example 9(e). In the same manner, 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methyl-malonic acid yield 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid (XV, R = H, $R^3$ = $CH_3$). Both the above compounds are converted to the corresponding -acetamide or -propionamide by the method described in Example 9(f).

(f) A mixture of 5-chloro-10,11-dihydro-5H-dibenzo[a,d] cycloheptene (13.8 g) and of the copper derivative of ethyl acetoacetate (9.7 g) is refluxed with stirring in benzene for 8 hours, cooled, ether is added, the precipitate is filtered off, the filtrate is successively washed with water, 10% sodium hydroxide, and water, dried with anhydrous sodium sulfate, and

evaporated. The residue is cyrstallized from petroleum ether (b.p. 40-60°C) to yield 2-(10,11-dihydro-5H-dibenz [a,d]cyclohepten-5-yl)-acetoacetic acid ethyl ester (XXII, R = $R^3$ = H, lower alkyl = $C_2H_5$) with m.p. 78-80°C. In the same manner, when using the copper salt of ethyl 2-methylacetoacetate as starting material and proceeding as above, 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methylacetoacetic acid ethyl ester (XXII, R = H, $R^3$ = $CH_3$, lower alkyl = $C_2H_5$) is obtained.

(g) A mixture of 2-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-acetoacetic acid ethyl ester (5.8 g)in ethanol (90 ml) and 50% aqueous sodium hydroxide (90 ml) is refluxed for 3 hours, the ethanol evaporated under reduced pressure, the residue cooled, and water is added. The solution is extracted with ether, the alkaline aqueous phase is acidified with 10% hydrochloride acid, extracted with ether, the ether extracts washed with water, dried with anhydrous sodium sulfate, and evaporated to (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-acetic acid (XV, R = $R^3$= H), identical with the compound obtained as described in Example 9(e). In the same manner, 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methylacetoacetic acid ethyl ester yields 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid (XV, R = H, $R^3$ = $CH_3$). Both the above compounds are converted to their corresponding -acetamides and -propionamides by the method described in Example 9(f).

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 5-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-malonic acid diethyl ester, or 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol, the correspondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-malonic acid, of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-methyl-malonic acid, of their respective diethyl esters, of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid, of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid, of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide and of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionamide are respectively obtained.

EXAMPLE 13

(a) A mixture of (10,11-dihydro-5H-dib nzo[a,d]-cyclohepten-5-yl)-acetic acid (5.0 g) and thionyl chloride (20 ml) is stirred for about one hour. Thionyl chloride is removed under reduced pressure at a temperature below 60°C. Cold acetone (about 150 ml) is added with stirring and cooling (ice-salt bath). Sodium azide (3.0 g) in 9 ml. of water is added over five minutes. The mixture is stirred for 1.5 hours, extracted with ether at low temperature (ice-cold water layer), the ether extract is carefully dried and evaporated under reduced pressure at room temperature, to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid azide, $\gamma_{max}^{CHCl_3}$ 2150 $cm^{-1}$.

Dry benzene is added, the mixture is refluxed, and the conversion of the azide to the corresponding isocyanate is followed by infrared spectrography. (10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylisocyanate (XXIV, R = $R^3$ = H), is obtained within about 20 minutes with $\gamma_{max}^{benzene}$ 2250 $cm^{-1}$ and is isolated by evaporation of the solvent under reduced pressure.

The isocyanate obtained as above is heated to about 80°C with approximately 6N hydrochloric acid (8 ml) for about 30 minutes. Ether is added, the precipitate is filtered, washed with ether, and dried to yield (10,11-dihydro-5H-dibenzo-[a,d]cycloheptene-5-yl)-methylamine hydrochloride, m.p. >275°C.

In the same manner, when using as starting materials an equivalent amount of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclo-

hept n-5-yl)-propionic acid and proceeding as ab ve there are obtain d 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid azide, 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylisocyanate, and 1-(10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)-ethylamine hydrochloride.

(b) A mixture of 50 g of 10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)-acetic acid and 50 ml of hydrazine hydrate (99-100%) is refluxed for 6.5 hours and the excess hydrazine hydrate is removed under reduced pressure. The residue is dissolved in 150 ml of isopropanol at 70°C with stirring. The clear colorless solution is cooled to 0°-5°C and the crystalline precipitat is collected by filtration, washed with cold isopropanol and dried to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid hydrazide, m.p. 143-145°C after crystallization from isopropanol.

Alternatively, a mixture of 50 g of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid and 60 ml of thionyl chloride is refluxed for 20 minutes with stirring. Excess thionyl chloride is removed under reduced pressure, 20 ml of methanol is added, refluxed for 30 minutes and the excess methanol removed under reduced pressure. Isopropanol (50 ml) and 75 ml of hydraxine hydrate (99-100%) are added and the mixture is refluxed with stirring overnight, evaporated to dryness, washed with 2 x 100 ml of n-hexane and dried, to yield, after crystallization from isopropanol, (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid hydrazide, identical with the compound obtained as described above.

As an ther alternative, a mixture of 26.6 g of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid methyl ester, obtained as described in Example 9(i), 7.5 ml of hydrazine hydrate (99-100%) and 25 ml of isopropanol is refluxed for 6 hours and allowed to stand at room temperature overnight. The crystalline precipitate is collected by filtration, washed with cold isopropanol and dried, to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid hydrazide with m.p. 143-145°C, identical with the compound obtained above, $\gamma_{max}^{CHCl_3}$ 3450, 3335, 1674, 1623 $cm^{-1}$.

In the same manner, when starting with equivalent amounts of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid or its methyl ester and proceeding as above there is obtained 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid hydrazide.

(c) A mixture of 12 g of 10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-acetic acid hydrazide and 150 ml of tetrahydrofuran is cooled to -5°C with stirring. Concentrated hydrochloric acid (37-38%, 18 ml) is added to the mixture and a clear solution is obtained. A solution of 7.5 g. of sodium nitrite in 20 ml of water is added dropwise with stirring to the reaction mixture and the temperature is maintained at -5 to 0°C for 1 hour. Infrared spectrography shows that eventually only the corresponding acetic acid azide ( $\gamma_{max}^{CHCl_3}$ 2150 $cm^{-1}$) is present, and thin layer chromatography confirms this. Cold water (100 ml) and toluene (250 ml) are added with stirring.

The organic layer is separated and the aqueous layer is extracted with 2 x 100 ml of toluene. The organic layer and the toluene extracts are combined, dried over anhydrous sodium sulfate overnight and evaporated under reduced pressure to about 100 ml. The toluene solution is slowly heated to reflux for 30 minutes with stirring (evolution of nitrogen), and then evaporated as above to about 30 ml. Infrared spectrography shows that eventually only 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylisocyanate ($\gamma^{CHCl_3}_{max}$ 2250 $cm^{-1}$) is present. Hydrochloric acid (6N, 15 ml) is added and the resultant mixture is heated at 80°C with stirring for 1 hour and the precipitate is collected by filtration, washed with n-hexane and dried to yield 10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylamine hydrochloride, identical with the same compound obtained as described in Example 13(a). In the same manner, when using as starting material 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid hydrazide and proceeding as above there is obtained 1-(10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)-ethylamine hydrochloride.

The methylamine or 1-ethylamine hydrochlorides obtained by the methods described above under (a) or (c) are converted by the process described in Example 5 to the free amines, which are identical with the methylamine and 1-ethylamine derivatives of formula IX obtained as described in Example 5(b), respectively.

(d) A mixture of 3 g of (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-acetamide and 30 ml of sodium hypobromite solution (4.1 g of bromine in a solution of 7.1 g of NaOH in

14.2 ml of water and 20 g of ice) is refluxed for 30 minutes with stirring. The reaction mixture is cooled to room temperature, extracted with 2 x 50 ml of benzene, the benzene extracts combined, dried over anhydrous sodium sulfate and evaporated to about 50 ml. Anhydrous hydrogen chloride is bubbled through the solution, the precipitate is collected by filtration, washed with anhydrous ether and dried, to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine hydrochloride, identical with the compound obtained as described in Examples 13(a) or (c). In the same manner when using an equivalent amount of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionamide as starting material there is obtained 1-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-ethylamine hydrochloride. Both the above hydrochloride salts are converted to the corresponding free amines by the method described in Example 5 and are identical with the methylamine and 1-ethylamine derivatives of formula IX obtained as described in Example 5(b), respectively.

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid, of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid or their respective methyl esters, of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetamide or or 2-(10,11-dihydro-5H-dibenzo[a,d]-

cyclohepten-5-yl)-propionamide, the correspondingly substituted 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-,2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid azides, of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid azides, of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid hydrazides, of 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid hydrazides, of (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylisocyanates, of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylisocyanates, of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine and of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine are respectively obtained.

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EXAMPLE 14

To 6 g of 3-chloro-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl-carboxamide (J. Med.Chem., 7, 88, 1964) in 60 ml of tetrahydrofuran are added 150 ml of a 1M solution of diborane in tetrahydrofuran, the reaction mixture is refluxed for five hours and acidified by addition of 10% aqueous hydrochloric acid. The precipitate is filtered, the filtrate is concentrated and filtered again, to yield 3-chloro-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine hydrochloride, with m.p. 300-310°C.

EXAMPLE 15

A solution of 10,11-dihydro-5H-dib nz [a,d]cycloh pten-5-one (20.0 g) in 150 ml of ethanol is mixed with 15 ml of nitromethane. With cooling to 0°C and with vigorous stirring an ice cold solution of 12g of potassium hydroxide in a mixture of water (30 ml) and ethanol (20 ml) is added dropwise after stirring for 30 minutes at 0°C the reaction mixture is added to stirred concentrated hydrochloric acid (100 ml) at -10°C. The precipitated product is filtered off, dissolved in benzene, dried with sodium sulfate, and the solvent evaporated, to yield (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-nitromethane (XXIII, R = $R^3$ = H). It is dissolved in tetrahydrofuran and refluxed with lithium aluminum hydride (12.0 g) for 24 hours. Addition of water, filtration of inorganic salts and evaporation of the solvent yields (10,11-dihydro-5H-dibenzo[a,d]cyclohept-5-yl)methylamine (IX, R= $R^1$ = $R^3$ = H) identical with the compound prepared as described in Example 5(b).

In the same manner, when using nitroethane instead of nitromethane and proceeding as above 1-(10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-ylidene)-nitroethane (XXIII, R = H, $R^3$ = $CH_3$) is obtained and reduced as described above to yield 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)ethylamine (IX, R = $R^1$ = H, $R^3$ = $CH_3$), also identical with the compound described in 5(b).

In the same manner, when using as starting material the 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3- methylsulfonyl, 3-tri-

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fluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one, the correspondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-flyoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine and 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine are obtained, identical with the same compounds described in Example 5 (c).

EXAMPLE 16

(a) (10,11-Dihydro-5H-dibenzo[a,d]cycloh pten-5-yl)-methylamine (10 g), ethyl bromide (21.2 g), potassium carbonate (40 g) and ethanol (100 ml) are combined and refluxed with vigorous stirring for 16 hours. The solvent is evaporated and the residue distributed between benzene and water. The benzene phase is dried with sodium sulfate and evaporated to give an oily residue. It is chromatographed on alumina to give N-ethyl-(10,11-dihydro-5H-dibenzo[a,d]cycloheptен-5-yl)methylamine (IX, R = $R^3$ = H, $R^1$ = $C_2H_5$), identical with the compound obtained as described in Example 7. In the same manner, when using 1-(10,11-dihydro-5H-dibenzo[a,d]cycloheptен-5-yl)ethylamine as starting material and proceeding as above there is obtained N-ethyl-1-(10,11-dihydro-5H-dibenzo[a,d]cycloheptен-5-yl)ethylamine (IX, R = H, $R^1$ = $C_2H_5$, $R^3$ = $CH_3$). Also in the same manner, but using methyl iodide, allyl bromide, cyclopentyl bromide, cyclohexylmethyl chloride, or benzyl chloride instead of ethyl bromide and proceeding as above, the N-methyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, and N-benzyl derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylamine and of 1-(10,11-dihydro-5H-dibenzo[a,d]-cycloheptен-5-yl)ethylamine are respectively obtained.

(b) Formic anhydride is prepared by heating at 50-60°C for 2 hours, formic acid (2.15 ml) and acetic anhydride ( 5.08 ml) cf. Huffman J. Org. Chem. 23, 727 (1958). The reaction mixture is cooled to 27° and (10,11-dihydro-5H-dibenzo[a,d]cycloheptен-5-yl)methylamine (5.6 g) is added over 15 minutes with vigorous stirring while maintaining the temperature below 39° with an

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ice bath. Stirring is continued for 20 hours at room temperature. The mixture is poured onto ice and the white precipitate is filtered and taken up in chloroform which is washed successively with dilute sodium bicarbonate and sodium chloride solutions. The chloroform is dried with anhydrous sodium sulfate and evaporated to yield N-formyl-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylamine, m.p. 109-110°C after crystallization from benzene-hexane.

A mixture of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (48 g) in 250 ml of pyridine and 30 ml of acetic anhydride is heated on the steam bath overnight. The solvent is removed under reduced pressure, the residue dissolved in chloroform, washed with water, and the solvent evaporated to yield N-acetyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine with m.p. 139°C after crystallization from benzene-hexane.

In the same manner, by using formic anhydride, acetic anhydride, propionic, cyclohexylcarboxylic, or benzoic acid chloride or anhydride, or by using 1-(10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)ethylamine instead of the above methylamine, the corresponding N-formyl, N-acetyl, N-propenoyl, N-cyclohexylcarbonyl, and N-benzoyl derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylamine or of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)ethylamine are respectively obtained.

(c) N-Formyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylamine (3.6 g) is refluxed under nitrogen with 30 ml of a 1 molar solution of diborane in tetrahydrofuran for 5 hours. Aqueous hydrochloric acid (20%, 100 ml) is added and the tetrahydrofuran is evaporated under reduced pressure. Aqueous sodium hydroxide (10%) is added until the solution is basic and the mixture is extracted with chloroform. After drying the chloroform layer with sodium sulfate evaporation of the solvent yields N-methyl-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)methylamine as an oil, characterized by an NMR bond at 143Hz and by its hydrochloride salt with m.p. 265-275°C

N-Acetyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylamine (5 g), lithium aluminum hydride (5 g) and tetrahydrofuran (60 ml) are refluxed for 24 hours. Addition of water, filtration and evaporation of the solvent gives N-ethyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylamine, identical with the same compound prepared as described in Example 7.

In the same manner, by treating the N-propenoyl, N-cyclohexylcarbonyl, or N-benzoyl derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylamine or of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)ethylamine with diborane or with lithium aluminum hydride, the corresponding N-allyl, N-cyclohexylmethyl, and N-benzyl derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylamine and of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)ethylamine are respectively obtained.

EXAMPLE 17

(a) 10,11-Dihydro-5H-dibenzo[a,d]cycloheptene-5-methylamine (10.0 g) is mixed with 40% aqueous formaldehyde (25.0 ml) and 1N hydrochloric acid (100 ml) and heated on the steam bath for three hours. The mixture is cooled, made alkaline with 2N sodium hydroxide and extracted with benzene. Washing, drying and evaporation of the benzene phase yields 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline (I, R = $R^1$ = $R^2$ = $R^3$ = H), m.p. 88-90°C. The hydrochloride salt is obtained by treating the above compound in ether solution with hydrogen chloride and has m.p. 280-284°C after crystallization from methanol-ether.

Alternatively, 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-methylamine hydrochloride (10.0 g) is dissolved in water (45 ml) and 40% aqueous formaldehyde (25.0 ml) is added. The mixture is heated on the steam bath for three hours, then cooled, made alkaline with 2N sodium hydroxide and extracted with benzene. Washing, drying and evaporation of the benzene phase gives the same compound as above, (I, R = $R^1$ = $R^2$ = $R^3$ = H).

(b) In the same manner, when using as starting materials 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)ethylamine or its hydrochloride salt and treating either compound with 40% aqueous formaldehyde as described above, there is obtained 1-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (I, R = $R^1$ = $R^2$ = H, $R^3$ = $CH_3$), $\gamma_{max}^{CHCl_3}$ 3000, 1520 $cm^{-1}$.

(c) In the same manner, when using as starting materials

(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylamine or its hydrochloride salt and treating either compound with acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, n-pentan-1-al, isopental-1-al (2-methylbutan-1-al), n-hexan-1-al, isohexan-1-al (4-methylpentan-1-al) n-heptan-1-al, n-octan-1-al, n-nonan-1-al, n-undecan-1-al, vinylacetaldehyde, cyclopropylaldehyde, cyclohexylacetaldehyde, benzaldehyde, or phenylacetaldehyde as described above, there are obtained 3-methyl-, 3-ethyl-, 3-propyl-, 3-isopropyl-, 3-n-butyl-, 3-isobutyl-, 3-n-amyl-, 3-isoamyl-, 3-n-hexyl-, 3-n-heptyl-, 3-n-octyl-, 3-n-decyl-, 3-allyl-, 3-cyclopropyl-, 3-cyclohexylmethyl-, 3-phenyl-, and 3-benzyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinoline, respectively.

(d) N-ethyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (5.8 g), obtained as described in Example 7, 40% aqueous formaldehyde (15 ml) and 1 N hydrochloric acid (60 ml) are heated together on the steam bath for four hours, the mixture cooled, made alkaline with 2 N sodium hydroxide, extracted with benzene, and the benzene extracts washed, dried, and evaporated to yield 2-ethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, m.p. 58.5-60°C after crystallization from ethanol. Treatment with hydrogen chloride in ether solution yields the hydrochloride salt, m.p. 238°C, after crystallization from isopropanol.

Similarly, when starting with N-methyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl or N-benzyl-(10,11-dihydro-

5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine and proceeding as above there are obtained 2-methyl-1,2,3,7,8,12b-hexahydro[6,7]-cyclohepta[1,2,3-d,e]isoquinoline, m.p. 90-91°C after crystallization from hexane, hydrochloride salt with m.p. 268-272°C prepared as above, and 2-allyl, 2-cyclopentyl, 2-cyclohexylmethyl, and 2-benzyl-1,2,3,7,8,12b-hexahydro-benzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, respectively.

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoro-methyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylamine, of its N-methyl or its N-ethyl derivatives, or of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine, the correspondingly substituted 6- or 9, 5- or 10-, 4- or 11-, or 12-methyl, 9,12-dimethyl, 4- or 11-t-butyl, 6- or 9-, 5- or 10- or 4- or 11-chloro, 4- or 11-fluoro, 4- or 11-bromo, 4,10- or 5,11-dibromo, 5- or 10-hydroxy or 4- or 11-hydroxy, 5- or 10-methoxy or 4- or 11-methoxy, 5- or 10-acetoxy, 4- or 11-methylthio, 4- or 11-methylsulfonyl, 4- or 11-trifluoromethyl, 12-amino, 12-methylamino, 4- or 11-dimethylaminosulfonyl, 4-bromo-11-dimethylaminosulfonyl or 11-bromo-4-dimethylaminosulfonyl, 4,11-dinitro and 4,9- or 6,11-dinitro derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline and of its 2-methyl, 2-ethyl, or 1-methyl derivatives are respectively obtained.

EXAMPLE 18

(a) (10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (11.15 gm) is dissolved in 60 ml of chlorobenzene and the mixture is saturated with anhydrous hydrogen chloride. Phosgene is bubbled through the suspension for 15 minutes and then the mixture is stirred at room temperature for two hours. The chlorobenzene solution is filtered and the solvent is removed under reduced pressure. The residual (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylisocyanate (XXIV, R = $R^3$ = H), identical with the compound described in Example 13, is dissolved in 25 ml of nitrobenzene and treated with anhydrous aluminum chloride (3.2 gm) followed by heating at 60 - 70° for one hour. Water is added, the organic phase is diluted with chloroform, dried with sodium sulfate and evaporated to dryness under reduced pressure. The residue is crystallized from a chloroform-hexane mixture to yield 1,2,3,7,8,12b-hexahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinolin-3-one (XXV, R = $R^1$ = $R^3$ = H), m.p. 173-175°C, $\nu_{max}^{CHCl_3}$ 1672 $cm^{-1}$.

In the same manner, when using 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine as the starting material there is obtained the intermediate 1-(10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)ethylisocyanate (XXIV, R = H, $R^3$ = $CH_3$), and 1-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolin-3-one (XXV, R = $R^1$ = H, $R^3$ = $CH_3$).

(b) (10,11-Dihydro-5H-dibenz [a,d]cycloh pten-5-yl)-acetic acid (18.5 gm) is mixed with 670 gm of polyphosphoric acid and heated with stirring on the steam bath for five hours, allowed to remain at 22°C for ten hours, and then poured onto cracked ice and extracted with benzene. The dark benzene phase is washed with dilute aqueous sodium hydroxide, then with water to yield an amber oil. Recrystallization from benzene yields 2-oxo-1,6,7,11b-tetrahydro-2H-dibenz[cd,h]azulene (XXVI, R = $R^3$ = H), m.p. 219-220°, which may be purified by high vacuum sublimation.

Alternatively, (10,11-dihydro-5H-dibenzo[a,d]cyclo-hepten-5-yl)-acetic acid is dissolved in 100 ml of anhydrous hydrogen fluoride. The solution has a blue color and is allowed to evaporate to dryness overnight. The residue is distributed between chloroform and 10% aqueous sodium hydroxide. The red chloroform phase is treated with charcoal (Nuchar), dried with anhydrous sodium sulfate, and evaporated to yield a yellow solid, m.p. 205-215°C, which is triturated with a mixture of 100 ml of hot hexane and 10 ml of benzene, cooled, and filtered to yield the same compound as above with m.p. 217.5-219°C.

In the same manner, when starting with 2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid and proceeding as above there is obtained 1-methyl-2-oxo-1,6,7,11b-tetrahydro-2H-dibenz[cd,h]azulene (XXVI, R = H, $R^3$ = $CH_3$).

2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propionic acid, the correspondingly substituted 6- or 9, 5- or 10-, 4- or 11-, or 12-methyl, 9,12-dimethyl, 4- or 11-t-butyl, 6- or 9-, 5- or 10- or 4- or 11-chloro, 4- or 11-fluoro, 4- or 11-bromo, 4,10- or 5,11-dibromo, 5- or 10-hydroxy or 4- or 11-hydroxy, 5- or 10-methoxy or 4- or 11-methoxy, 5- or 10-acetoxy, 4- or 11-methylthio, 4- or 11-methylsulfonyl, 4- or 11-trifluoromethyl, 12-amino, 12-methylamino, 4- or 11-dimethylaminosulfonyl, 4-bromo-11-dimethylaminosulfonyl or 11-bromo-4-dimethylaminosulfonyl, 4,11-dinitro and 4,9- or 6,11-dinitro derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-one are obtained.

(c) 2-Oxo-1,6,7,11b-tetrahydro-2H-dibenz[cd,h]azul n (4.5 g) is dissolved in molten trichloroacetic acid (45 g) and sodium azide (2.4 g) is added. The mixture is heated on the steam bath for 30 minutes and then allowed to remain at 22°C for 16 hours. It is then poured into cold water, made alkaline with ammonium hydroxide and extracted with chloroform. The chloroform phase is dried with anhydrous sodium sulfate and evaporated to dryness to yield 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-one (XXV, R = $R^1$ = $R^3$ = H), identical with the said compound obtained as described in Example 18 (a).

In the same manner, when starting with 1-methyl-2-oxo-1,6,7,11b-tetrahydro-2H-dibenz[cd,h]azulene and proceeding as above, 1-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinolin-3-one (XXV, R = $R^1$ = H, $R^3$ = $CH_3$) is obtained, identical with the same compound obtained in Example 18(a).

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoro-methyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylamine, of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine, of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-acetic acid, or of

EXAMPLE 19

(a) 1,2,3,7,8,12b-Hexahydrobenzo[6,7]cyclohepta[1,2,3-de]-isoquinolin-3-one (2.1 g) and lithium aluminum hydride (1.0 g) are combined in tetrahydrofuran (40 ml) and refluxed for 16 hours. The excess lithium aluminum hydride is destroyed by addition of water and the organic phase is separated after removal of precipitated inorganic salts by filtration. It is dried and evaporated to dryness to yield 1,2,3,7,8,12b-hexahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinoline (I, R = $R^1$ = $R^2$ = $R^3$ = H), identical with the same compound obtained as described in Example 17(a).

In the same manner, when starting with 1-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-one and proceeding as above there is obtained 1-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline.

(b) 1,2,3,7,8,12b-Hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolin-3-one (25.0 g) is treated with sodium hydride (5.0 g of a 50% suspension in mineral oil) in dimethoxyethane (100 ml) at 90° for 4 hours in an atmosphere of nitrogen. To the red suspension of the sodium salt is added ethyl bromide (20 g) and the mixture is refluxed for 14 hours. The solvent is evaporated and the residue is distributed between water and chloroform. The chloroform phase is dried with sodium sulfate and evaporated to give 2-ethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinolin-3-one, $\nu_{max}^{CHCl_3}$ 1660 $cm^{-1}$.

In the same manner, when starting with 1-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-

3-on and proceeding as ab v , there is obtained 1-methyl-2-ethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-one.

Again in the same manner, when using methyl, allyl, cyclopentyl, cyclohexylmethyl, or benzyl chloride, bromide, or iodide instead of ethyl bromide and proceeding as above, the 2-methyl, 2-allyl, 2-cyclopentyl, 2-cyclohexylmethyl, and 2-benzyl derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolin-3-one and of its 1-methyl derivative are respectively obtained.

(c) 1,2,3,7,8,12b-Hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolin-3-one (3.8 gm) is dissolved in a mixture of 30 ml of acetic anhydride and 15 ml of pyridine and refluxed for 2 hours. The mixture is concentrated under reduced pressure and the residue distributed between water and chloroform. The organic phase yields a gum which is crystallized from acetone to yield 2-acetyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolin-3-one with m.p. 199-200°C.

In the same manner, by using the 1-methyl derivative of the above starting material and proceeding as above, 1-methyl-2-acetyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolin-3-one is obtained.

In the same manner, but using propenoic, cyclohexylcarboxylic, or benzoic acid anhydride or chloride and proceeding as above the corresponding 2-propenoyl, 2-cyclohexylcarboxyl, and 2-benzoyl derivatives of 1,2,3,7,8,21b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-one and of its 1-methyl derivative are respectively obtained.

(d) 2-Acetyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinolin-3-one (2.2 g) and lithium aluminum hydride (1.8 g) are combined in tetrahydrofuran (40 ml) and refluxed for 16 hours. The excess lithium aluminum hydride is destroyed by addition of water and the organic phase is separated after removal of precipitated inorganic salts by filtration. It is dried and evaporated to dryness to yield 2-ethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, identical with the compound obtained as described in Example 17(d). The same compound is also obtained when using 2-ethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-one as starting material and proceeding as above.

In the same manner, when using as starting materials the 2-methyl, 2-allyl or 2-propenoyl, 2-cyclopentyl, 2-cyclohexyl-methyl or 2-cyclohexylcarbonyl, 2-benzyl or 2-benzoyl derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-one or of its 1-methyl derivative, there are obtained 2-methyl-, 2-allyl-, 2-cyclopentyl-, 2-cyclohexylmethyl, and 2-benzyl-1,2,3,7,8,21b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline and their 1-methyl derivatives, respectively.

Also in the same manner, when using as starting materials the 6- or 9, 5- or 10-, 4- or 11-, or 12-methyl, 9,12-dimethyl, 4- or 11-t-butyl, 6- or 9-, 5- or 10- or 4- or 11-chloro, 4- or 11-fluoro, 4- or 11-bromo, 4,10- or 5,11-dibromo, 5- or 10-hydroxy or 4- or 11-hydroxy, 5- or 10-methoxy or 4- or 11-methoxy, 5- or 10-acetoxy, 4- or 11-methylthio, 4- or 11-methylsulfonyl, 4- or 11-trifluoromethyl, 12-amino, 12-methylamino, 4- or 11-dimethyl-

aminosulfonyl, 4-bromo-11-dimethylaminosulfonyl or 11-bromo-4-dimethylaminosulfonyl, 4,11-dinitro and 4,9- or 6,11-dinitr derivatives of the 2-methyl-, 2-ethyl or 2-acetyl-, 2-allyl- or 2-propenoyl-, 2-cyclopentyl-, 2-cyclohexylmethyl- or 2-cyclohexylcarboxyl-, 2-benzyl- or 2-benzoyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinolin-3-ones listed above, the correspondingly substituted 2-methyl-, 2-ethyl-, 2-allyl-, 2-cyclopentyl-, 2-cyclohexylmethyl-, and 2-benzyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolines are respectively obtained.

EXAMPLE 20

(a) 10,11-Dihydro-5H-dibenzo[a,d]cyclohept n-5-yl-methylamine (45 g) is dissolved in ethyl formate (150 ml.) and allowed to stand at room temperature for 12 hours. The excess ethyl formate is removed by distillation under reduced pressure, the residue is dissolved in benzene and washed with 2N hydrochloric acid. The organic phase is dried with sodium carbonate, evaporated and the residue crystallized from an ethanol-ether mixture to yield N-formyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (XXVII, R = $R^1$ = $R^3$ = H, Y = CHO), m.p. 109-111°, $\nu_{max}^{CHCl_3}$ 1670 $cm^{-1}$.

(b) A mixture of formic acid (2.15 ml) and acetic anhydride (5.08 ml) is heated at 50 - 60° for 2 hours. The mixture is cooled to 27° and 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)—ethylamine (5.6 gm) is added with vigorous stirring over 15 minutes. The mixture is stirred overnight at room temperature and then poured onto cracked ice. The resulting while precipitate is dissolved in chloroform and washed with dilute sodium bicarbonate solution, then with water. Drying with anhydrous sodium sulfate and evaporation of the solvent yields a solid residue which on crystallization from an ethanol-ether mixture yields N-formyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine.

(c) N-ethyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, obtained as described in Example 7 (7.0 g) is treated with formic acetic anhydride (prepared from acetic anhydride (12.8 ml) and 15.9 ml formic acid) at 22°C for 16 hours.

The reaction mixture is poured into ice-water and extracted with chloroform. The chloroform phase is washed with sodium bicarbonate soluti n, dried with s dium sulfate and vaporated und r reduced pressure to yield N-formyl N-ethyl-(10,11-dihydr - 5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, $\nu_{max}^{CHCl_3}$ 1650 $cm^{-1}$.

(d) Formic anhydride is prepared by heating at 50-60° for two hours 2.2 ml of formic acid and 5 ml of acetic anhydride. This mixture is added to 4.5 g of 3-chloro-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, prepared as described in Example 14, keeping the temperature below 30°. The reaction mixture is left at room temperature overnight, poured on water, extracted with ethyl acetate and washed with 10% sodium bicarbonate solution. After removal of the solvent the residual oil is crystallized from ether or cyclohexane/benzene, to yield N-formyl-(3-chloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, m.p. 135-139°C.

In the same manner, as described above under (a), (b), (c) or (d), but using chloral or formic acid instead of ethyl chloroformate or formic-acetic anhydride, the above compounds are also obtained.

(e) In the same manner as described above under (a), (b), (c) or (d), but using as starting material the N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl or N-benzyl derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine or of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine, there are obtained the N-formyl-N-methyl, N-formyl-N-ethyl (see under (c), N-formyl-N-allyl, N-formyl-N-cyclopentyl, N-formyl-N-cyclohexylbutyl, and N-formyl-N-benzyl derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine and of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine, respectively.

(f) Alternatively, (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)methylis cyanate (2.2 g), btain d as described in Examples 13(a) or 18(a), is dissolved in toluene (25 ml) and cool d to -20°C. Formic acid (1 ml, 88%) is added dropwise with stirring, the mixture is allowed to come to room temperature, formic acid (1 ml, 88%) is added and the mixture is heated to 35-40°C for 15 minutes. Evaporation under reduced pressure to about 10 ml, washing with water, evaporation to dryness, and crystallization from benzene-hexane yields N-formyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, identical with the same compound obtained as described in Example 20(a). In the same manner, when starting with 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)ethylisocyanate there is obtained N-formyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine, identical with the same compound obtained as described in Example 20(b).

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, or 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, or their N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives, the correspondingly substituted 1-, 2-, 3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-,2-, or 3-chloro(see under (d), 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitr r 3,9-dinitro derivativ s of the N-formyl d rivatives of the above compounds are respectiv ly btained.

EXAMPLE 21

A mixture of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (48 g) in 250 ml of pyridine and 30 ml of acetyl chloride is heated on the steam bath overnight. The solvent is removed under reduced pressure, the residue dissolved in chloroform, washed with water, the solvent evaporated, and the residue crystallized from benzene-hexane, to yield N-acetyl-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylamine with m.p. 139°C.

In the same manner, by using 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine as the starting material, there is obtained N-acetyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine.

In the same manner, when starting with (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine, or their N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives and reacting with acetic acid, propionic acid, butyric acid, isobutyric acid, pentanoic acid, isopentanoic acid, hexanoic acid, isohexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, undecanoic acid, propenoic acid, methoxyacetic acid, cyclopropylcarboxylic acid, cyclohexylacetic acid, benzoic acid, or phenylacetic acid chloride or anhydride, there are respectively obtained the N-acetyl, N-propionyl, N-butanoyl, N-isobutanoyl, N-pentanoyl, N-isopentanoyl, N-hexanoyl, N-isohexanoyl,

N-heptanoyl, N-octanoyl, N-nonanoyl, N-undecanoyl, N-propenoyl, N-methoxyacetyl, N-cyclopropylcarbonyl, N-cyclohexylacetyl, N-benzoyl, and N-phenylacetyl derivatives of (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylamine, (XXVIIb, R = $R^1$ = $R^3$ = H, Y = acyl as listed above), 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine (XXVII b, R = $R^1$ = H, $R^3$ = $CH_3$, Y = acyl as listed above) and the N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, and N-benzyl derivatives of the compounds listed above.

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine, or of their N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives, the correspondingly substituted 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-,2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of the N-acetyl, N-propionyl, N-butanoyl,

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N-is butanoyl,N-pentanoyl, N-isopentanoyl, N-hexanoyl, N-isohexanoyl, N-heptanoyl, N-octanoyl, N-nonanoyl, N-undecanoyl, N-propenoyl, N-methoxyacetyl, N-cyclopropylcarbonyl, N-cyclohexylacetyl, N-benzoyl, and N-phenylacetyl derivatives of (10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylamine, of 1-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-ethylamine and of their N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, and N-benzyl derivatives are respectively obtained.

EXAMPLE 22

(a) To (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (6.7 g) dissolved in 80 ml of ethylene dichloride is added 33 ml of 1N aqueous sodium hydroxide. The mixture is cooled to 0°C and ethyl chloroformate (3.58 gm) dissolved in 40 ml of ethylene dichloride is added over 15 minutes. The reaction mixture is kept at 0°C for 15 minutes, then at 22°C for 90 minutes. The organic phase is washed successively with water, 2N hydrochloric acid, water, 5% aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried with sodium carbonate and evaporated to yield N-carbethoxy-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylamine (XXVII c, $R = R^1 = R^3 = H$, $Y = COOC_2H_5$) as a solid) $\nu_{max}^{CHCl_3}$ 1715 $cm^{-1}$, m.p. 77-79° when crystallized from an ethyl acetate-hexane mixture.

In the same manner, when starting with 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine and proceeding as above, there is obtained N-carbethoxy-1-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-ethylamine. Also in the same manner, when starting with the N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives of the above starting materials, the N-carbethoxy derivatives thereof are obtained respectively.

(b) N-Carbethoxy 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine (1.0 g) is dissolved in 20 g polyphosphoric acid and heated at 120-150°C for 2 hours. The reaction mixture is distributed between water and chloroform. The organic phase is washed with dilute aqueous sodium hydroxide and with water.

Drying and evaporation yields a residue which on crystallization from a chloroform-hexane mixture yields 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-one with m.p. 173-175°C, $\nu_{max}^{CHCl_3}$ 1672 $cm^{-1}$, identical with the compound of formula XXV (R = $R^1$ = $R^3$ = H) obtained as described in Example 18(a) and (c).

(c) N-Carbethoxy 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl methylamine (1.0 g) is dissolved in xylene (25 ml) containing phosphorus pentoxide (5.0 g) and phosphorus oxychloride (10.0 g). The mixture is refluxed for 3 hours, benzene is added and the mixture is washed with 5% aqueous sodium hydroxide and with water. The organic phase is dried and evaporated to yield 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolin-3-one as a crystalline solid from a chloroform-hexane mixture, having identical properties to samples prepared according to part (b) above.

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine of 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine or of their N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl or N-benzyl derivatives, reacting any of the above compounds with

ethyl chloroformate to obtain the corresponding N-carbethoxy derivatives, respectively, and treating said last-named compounds with polyphosphoric acid or with phosphorus pentoxide and phosphorus oxychloride as above, there are obtained the correspondingly substituted 6- or 9, 5- or 10-, 4- or 11-, or 12-methyl, 9,12-dimethyl, 4- or 11-t-butyl, 6- or 9-, 5- or 10- or 4- or 11-chloro, 4- or 11-fluoro, 4- or 11-bromo, 4,10- or 5,11-dibromo, 5- or 10-hydroxy or 4- or 11-hydroxy, 5- or 10-methoxy or 4- or 11-methoxy, 5- or 10-acetoxy, 4- or 11-methylthio, 4- or 11-methylsulfonyl, 4- or 11-trifluoromethyl, 12-amino, 12-methylamino, 4- or 11-dimethylaminosulfonyl, 4-bromo-11-dimethylaminosulfonyl or 11-bromo-4-dimethylaminosulfonyl, 4,11-dinitro and 4,9- or 6,11-dinitro derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-ones (XXV) and their 2-methyl, 2-ethyl, 2-allyl, 2-cyclopentyl, 2-cyclohexylmethyl, and 2-benzyl derivatives, respectively.

The conversion of the above derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolin-3-one to the corresponding derivatives of 1,2,3,7,812b-hexahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinoline is described in Example 19 (a) and (d).

EXAMPLE 23

(a) N-Formyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine obtained as described in Example 20 (a) (1.26 g), is added to polyphosphoric acid (15 g) at 110°C. The temperature of the mixture is raised to 150 ± 5°C and kept there for one hour. The mixture is poured onto crushed ice and the resultant precipitate is dissolved in chloroform. Drying with anhydrous sodium sulfate and removal of the solvent under reduced pressure yields a residue which, on crystallization from benzene, yields 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline (XXVIII, R = $R^2$ = $R^3$ = H), m.p. 109-110°, $\nu_{max}^{CHCl_3}$ 1640 $cm^{-1}$, $\lambda_{max}^{EtOH}$ 293, ε 10200. Treatment with ethereal hydrogen chloride yields the hydrochloride salt, m.p. 205-207°C after crystallization from methanol-ether.

(b) A mixture of 1 g of N-formyl-(3-chloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine obtained as described in Example 20 (d) and 15 g of polyphosphoric acid is heated to 150°C, left at this temperature for one hour, poured onto ice, made basic with potassium hydroxide and extracted with ethyl acetate to give an oil which is crystallized from benzene to yield 11-chloro-1,7,8,12b-tetrahydrobenzo[6,7]-cyclohept-[1,2,3-d,e]isoquinoline (XXVIII, R = 11-Cl, $R^2$ = $R^3$ = H) m.p. 150-154°C. The hydrochloride salt is prepared with ethereal hydrogen chloride and has m.p. 210-215°C.

(c) A mixture of 43 g of N-acetyl-(10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)-methylamine, obtained as described in Example 21, and 150 g of polyphosphoric acid is heated to 150°C

for tw hours, poured on iced s dium hydroxide solution (ca. 20%), and extracted with ethyl acetate. Washing with water, drying with anhydrous sodium sulfate, and evaporation of the solvent yields 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (XXVIII, R = $R^3$ = H, $R^2$ = $CH_3$), m.p. 132°C after crystallization from benzene-hexane.

In the same manner, by using as starting material the N-formyl or N-acetyl derivatives of 1-(10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-yl)-ethylamine, and proceeding as above, there are obtained 1-methyl and 1,3-dimethyl-1,7,8,12b-tetrahydrobenzo-[6,7]cyclohepta[1,2,3-d,e]isoquinoline, respectively.

(d) Again in the same manner, when starting with N-propionyl-, N-butanoyl-, N-isobutanoyl-, N-pentanoyl-, N-isopentanoyl-, N-hexanoyl-, N-isohexanoyl-, N-heptanoyl-, N-octanoyl-, N-nonanoyl-, N-undecanoyl-, N-propenoyl-, N-methoxyacetyl-, N-cyclopropylcarbonyl-, N-cyclohexylacetyl-, N-benzoyl-, or N-phenylacetyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, or -1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine and treating any of said compounds with polyphosphoric acid, there are obtained, respectively, the Schiff bases of formula XXVIII 1,7,8,12b-tetra-hydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline (XXVIII, R = $R^2$ = $R^3$ = H), 1-methyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (XXVIII, R = $R^2$ = H, $R^3$ = $CH_3$) and their respective 3-ethyl, 3-propyl, 3-isopropyl, 3-butyl, 3-isobutyl, 3-anyl, 3-isoanyl, 3-hexyl, 3-heptyl, 3-octyl, 3-decyl, 3-allyl, 3-methoxymethyl, 3-cyclopropyl, 3-cyclohexylmethyl, 3-phenyl, and 3-benzyl derivatives.

In th sam manner, wh n using as starting mat rial the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of N-formyl-, N-acetyl-, N-propionyl-, N-butanoyl-, N-isobutanoyl-, N-pentanoyl-, N-isopentanoyl-, N-hexanoyl-, N-isohexanoyl-, N-heptanoyl-, N-octanoyl-, N-nonanoyl-, N-undecanoyl-, N-propenoyl-, N-methoxyacetyl-, N-cyclopropylcarbonyl-, N-cyclohexylacetyl-, N-benzoyl-, or N-phenylacetyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine, or -1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine and treating any of said compounds with polyphosphoric acid, there are obtained, respectively, the 6- or 9, 5- or 10-, 4- or 11-, or 12-methyl, 9,12-dimethyl, 4- or 11-t-butyl, 6- or 9-, 5- or 10- or 4- or 11-chloro, 4- or 11-fluoro, 4- or 11-bromo, 4,10- or 5,11-dibromo, 5- or 10-hydroxy or 4- or 11-hydroxy, 5- or 10-methoxy or 4- or 11-methoxy, 5- or 10-acetoxy, 4- or 11-methylthio, 4- or 11-methylsulfonyl, 4- or 11-trifluoromethyl, 12-amino, 12-methylamino, 4- or 11-dimethylaminosulfonyl, 4-bromo-11-dimethylaminosulfonyl or 11-bromo-4-dimethylaminosulfonyl, 4,11-dinitro and 4,9- or 6,11-dinitro derivatives of 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, of their respective 1-methyl derivatives, and of their respective 3-methyl, 3-ethyl, 3-propyl, 3-isopropyl, 3-butyl, 3-isobutyl, 3-anyl, 3-isoanyl, 3-hexyl, 3-heptyl, 3-octyl, 3-decyl, 3-allyl, 3-m thoxymethyl, 3-cyclopropyl, 3-cyclohexylmethyl, 3-phenyl, and 3-benzyl derivatives.

EXAMPLE 24

(a) 1,7,8,12b-Tetrahydrobenz [6,7]cyclohepta[1,2,3-d, ]-isoquinoline (2.0 g) obtained as described in Example 23 (a) is dissolved in ethanol (25 ml) and sodium borohydride (1.0 g) is added. The mixture is refluxed for four hours, then evaporated to dryness. The residue is distributed between water and chloroform. Drying and evaporating the chloroform phase yields 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (I, R = $R^1$ = $R^2$ = $R^3$ = H), m.p. 88-90°C. The hydrochloride salt is prepared from the above base with hydrogen chloride in ether solution. It is crystallized from a methanol-ether mixture and has m.p. 280-284°C. Both the above compound and its hydrochloride salt are identical with the same compound prepared as described in Example 17(a).

(b) 1,7,8,12b-Tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (1.0 g) is dissolved in tetrahydrofuran (30 ml) containing lithium aluminum hydride (1.0 g). The mixture is refluxed for 6 hours, water is added, the organic phase is separated, dried and evaporated, to yield the product, identical in all respects with the compound identified above.

(c) 1,7,8,12b-Tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (1.95 g) is dissolved in a mixture of 2N hydrochloric acid (42.4 ml) and glacial acetic acid (200 ml). Platinum oxide catalyst (1.0 g) is added and the mixture is hydrogenated at room temperature at 50 p.s.i. The theoretical amount of hydrogen is consumed in three minutes. The catalyst and solvents are removed and the resulting residue is distributed between chloroform and aqueous sodium hydroxide solution.

Washing, drying and evaporating th chloroform phas gives the pr duct, id ntical in all respects with the compound identified abov .

(d) A mixture of 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinoline (6.0 g), Raney nickel (25 g), and anhydrous ethanol (100 ml) is refluxed with stirring for 3 hours, filtered, and the filtrate evaporated to dryness under reduced pressure to yield 2-ethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline, from which the hydrochloride salt is prepared by treatment with hydrogen chloride in toluene solution. Both compounds are identical with the same compounds obtained as described in Example 17(d).

(e) In the same manner, when using as starting materials any of the substituted 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinolines obtained as described in Example 23(d) and proceeding as above, there are obtained the correspondingly substituted 6- or 9, 5- or 10-, 4- or 11-, or 12-methyl, 9,12-dimethyl, 4- or 11-t-butyl, 6- or 9-, 5- or 10- or 4- or 11-chloro, 4- or 11-fluoro, 4- or 11-bromo, 4,10- or 5,11-dibromo, 5- or 10-hydroxy or 4- or 11-hydroxy, 5- or 10-methoxy or 4- or 11-methoxy, 5- or 10-acetoxy, 4- or 11-methylthio, 4- or 11-methylsulfonyl, 4- or 11-trifluoromethyl, 12-amino, 12-methylamino, 4- or 11-dimethylaminosulfonyl, 4-bromo-11-dimethylaminosulfonyl or 11-bromo-4-dimethylaminosulfonyl, 4,11-dinitro and 4,9- or 6,11-dinitro derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, or their respective 1-methyl derivatives, and of their respective 3-methyl, 3-ethyl, 3-propyl, 3-isopropyl, 3-butyl, 3-isobutyl, 3-anyl, 3-isoanyl, 3-hexyl, 3-heptyl, 3-octyl, 3-decyl, 3-allyl, 3-methoxymethyl, 3-cyclopropyl, 3-cyclohexyl-methyl, 3-phenyl, and 3-benzyl derivatives.

EXAMPLE 25

(a) 1,2,3,7,8,12b-H xahydrob nzo[6,7]cyclohepta[1,2,3-d, ]-isoquinoline (1.17 gm, 0.005 moles), obtained as described in Examples 17(a) or 24(a), is dissolved in 30 ml of methanol, cooled to 0° and treated dropwise with 7.53 ml of 4.95% sodium hypochlorite (0.665 M, 0.005 moles) resulting in an exothermic reaction and the formation of a precipitate. The mixture is stirred one hour at room temperature, then treated dropwise with 37.5 ml of 2N sodium hydroxide (0.075 moles) and refluxed for 45 minutes. After stirring at room temperature overnight, the methanol is evaporated and the residue distributed between chloroform and water. The chloroform phase is dried with anhydrous sodium sulfate and evaporated to yield a yellow oil, which is dissolved in ether and treated with powdered carbon dioxide. The clear solution is evaporated to give a solid. Crystallization from acetonitrile yields 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline (XVIII, $R = R^2 = R^3 = H$) identical with the same compound obtained as described in Example 23(a).

(b) In the same manner, by using as starting material any of the derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline obtained as described in Examples 17 and 24 and proceeding as above, there are obtained the corresponding derivatives of 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinoline described in Example 23.

EXAMPLE 26

(a) One equivalent f 1,7,8,12b-t trahydrob nzo[6,7]-cyclohepta[1,2,3-d,e]isoquinoline, obtained as described in Example 23(a), is dissolved in 25 parts w/v of tetrahydrofuran, 1.5 equivalents of n-butyl magnesium bromide or n-butyllithium are added and the mixture is refluxed for 8 hours. Cooling, addition of 20% aqueous ammonium chloride solution, extraction with ether, washing, drying, and evaporating the solvent yields 3-butyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline characterized by NMR ($CDCl_3$) 0.95 δ (terminal $CH_3$), 1.87 δ (NH), 4.40 δ (H at position 12b). The hydrochloride salt is prepared with ethereal hydrogen chloride and has m.p. 250°C.

(b) In the same manner, by using methyl, ethyl, propyl, isopropyl, isobutyl, amyl, isoamyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, allyl, methoxymethyl, cyclopropyl, cyclohexyl-methyl, phenyl, or benzyl Grignard reagents, lithium, or cadmium derivatives, and reacting them as described above with 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline or with any of its derivatives described in Example 23 d, the correspondingly substituted derivatives of 1,2,3,7,8,12b-hexa-hydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline described in Example 17 are obtained.

EXAMPLE 27

(a) N-Ethyl-N-formyl-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-methylamine (10.0 g) is dissolved in toluene (100 ml) and phosphorus oxychloride (25 ml) is added. The mixture is refluxed for 16 hours, cooled, and diluted with 600 ml of hexane. The precipitated material is filtered off, washed with ether and dried, to yield 2-ethyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolinium phosphate (XXIX, $R = R^2 = R^3 = H$, $R^1 = C_2H_5$, $Z^- = 1/2\ HPO_4^{--}$) $\lambda_{max}^{EtOH}$ 292 mμ, ε 13,200.

(b) In the same manner, when starting with the N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives of N-formyl-, N-acetyl-, N-propionyl-, N-butanoyl-, N-isobutanoyl-, N-pentanoyl-, N-isopentanoyl-, N-hexanoyl-, N-isohexanoyl-, N-heptanoyl-, N-octanoyl-, N-nonanoyl-, N-undecanoyl-, N-propenoyl-, N-methoxyacetyl-, N-cyclopropylcarbonyl-, N-cyclohexylacetyl-, N-benzoyl-, or N-phenylacetyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine or -1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine and treating with phosphorus oxychloride, polyphosphoric acid or ester, phosphorus pentoxide, or mixtures thereof, there are obtained, respectively, the quaternary Schiff base salts of the formula XXIX 2-methyl-, 2-ethyl, 2-allyl, 2-cyclopentyl-, 2-cyclohexylmethyl, and 2-benzyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolinium phosphate (XXIX, $R = R^2 = R^3 = H$, $R^1$ = methyl, ethyl, allyl, cyclopentyl,

cyclohexylmethyl, and benzyl), 1,2-dimethyl-, 1-methyl-2-ethyl-, 1-methyl-2-allyl-, 1-methyl-2-cyclopentyl-, 1-methyl-2-cyclohexylmethyl-, and 1-methyl-2-benzyl-1,7,8,12b-tetrahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinolinium phosphate (XXIX, R = $R^2$ = H, $R^3$ = $CH_3$, $R^1$ = methyl, ethyl, allyl, cyclopentyl, cyclohexylmethyl, and benzyl), and their respective 3-methyl, 3-ethyl, 3-propyl, 3-isopropyl, 3-butyl, 3-isobutyl, 3-amyl, 3-isoamyl, 3-hexyl, 3-heptyl, 3-octyl, 3-decyl, 3-allyl, 3-methoxymethyl, 3-cyclopropyl, 3-cyclohexylmethyl, 3-phenyl, and 3-benzyl derivatives.

In the same manner, when using as starting material the 1-,2-,3-, or 4-methyl, 1,4-dimethyl, 3-t-butyl, 1-, 2-, or 3-chloro, 3-fluoro, 3-bromo, 2,7-dibromo, 2- or 3-hydroxy, 2- or 3-methoxy, 2-acetoxy, 3-methylthio, 3-methylsulfonyl, 3-trifluoromethyl, 4-amino, 4-methylamino, 3-dimethylaminosulfonyl, 3-bromo-7-dimethylaminosulfonyl, 3,7-dinitro or 3,9-dinitro derivatives of the N-methyl, N-ethyl, N-allyl, N-cyclopentyl, N-cyclohexylmethyl, or N-benzyl derivatives of N-formyl-, N-acetyl-, N-propionyl-, N-butanoyl-, N-isobutanoyl-, N-pentanoyl-, N-isopentanoyl-, N-hexanoyl-, N-isohexanoyl-, N-heptanoyl-, N-octanoyl-, N-nonanoyl-, N-undecanoyl-, N-propenoyl-, N-methoxyacetyl-, N-cyclopropylcarbonyl-, N-cyclohexylacetyl-, N-benzoyl-, or N-phenylacetyl-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methylamine or -1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-ethylamine and treating with phosphorus oxychloride, polyphosphoric acid or ester, phosphorus pentoxide, or mixtures thereof, there are

obtained, respectively, the 2-methyl, 2-ethyl, 2-allyl, 2-cyclopentyl, 2-cyclohexylmethyl, or 2-benzyl derivatives and their 1-methyl derivatives and their 3-methyl, 3-ethyl, 3-propyl, 3-isopropyl, 3-butyl, 3-isobutyl, 3-amyl, 3-isoamyl, 3-hexyl, 3-heptyl, 3-octyl, 3-decyl, 3-allyl, 3-methoxymethyl, 3-cyclopropyl, 3-cyclohexylmethyl, 3-phenyl, and 3-benzyl derivatives, of the 6- or 9, 5- or 10-, 4- or 11-, or 12-methyl, 9,12-dimethyl, 4- or 11-t-butyl, 6- or 9-, 5- or 10- or 4- or 11-chloro, 4- or 11-fluoro, 4- or 11-bromo, 4,10- or 5,11-dibromo, 5- or 10-hydroxy or 4- or 11-hydroxy, 5- or 10-methoxy or 4- or 11-methoxy, 5- or 10-acetoxy, 4- or 11-methylthio, 4- or 11-methylsulfonyl, 4- or 11-trifluoromethyl, 12-amino, 12-methylamino, 4- or 11-dimethylaminosulfonyl, 4-bromo-11-dimethylaminosulfonyl or 11-bromo-4-dimethylaminosulfonyl, 4,11-dinitro and 4,9- or 6,11-dinitro derivatives of 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolinium phosphate.

(c) To a solution of 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline (20.0 gm., 0.086 m) in 250 ml acetone is added 32 ml methyl iodide and the mixture is stirred to yield an oil. The mixture is refluxed for 2 hours and stirred at room temperature overnight to yield yellow crystals which are removed by filtration. Recrystallization from 300 ml 95% ethanol yields 2-methyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolinium iodide (XXIX, $R = R^2 = R^3 = H$, $R^1 = CH_3$, $Z^- = I^-$)

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m.p. 214-217°C; $\lambda_{max}^{EtOH}$ 290 mμ, ε 14,250; $\nu_{max}^{KBr}$ 1666 $cm^{-1}$

In the same manner, when using ethyl bromide instead of methyl iodide there is obtained 2-ethyl-1,7,7,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolinium bromide, m.p. 210°C. When using dimethyl or diethyl sulfate instead of methyl iodide or ethyl bromide, the sulfate salts of the above quaternary Schiff bases are obtained.

(d) A solution of 1 g of 11-chloro-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, obtained as described in Example 23(b) in 25 ml of acetone is refluxed for one hour with 5 ml of ethyl iodide. The precipitate is filtered and recrystallized from ethanol, to yield 11-chloro-2-ethyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohept[1,2,3-d,e]-isoquinolinium iodide, m.p. 218-222°C.

In the same manner, but using methyl iodide instead of ethyl iodide, there is obtained 11-chloro-2-methyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolinium iodide, m.p. 227-232°C.

(e) In the same manner, by using as starting material any of the derivatives of 1,7,8,12b-tetrahydro[6,7]cyclohepta-[1,2,3-d,e]isoquinoline obtained as described in Example 23 and reacting them with methyl, ethyl, allyl, cyclopentyl, cyclohexylmethyl, or benzyl chloride, bromide, iodide, or sulfate, the correspondingly substituted 2-methyl-, 2-ethyl-, 2-allyl-, 2-cyclopentyl-, 2-cyclohexylmethyl-, and 2-benzyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolinium chlorides, bromides, iodid s, and sulfat s are respectively btained.

EXAMPLE 28

(a) 2-Ethyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinolinium phosphate or bromide (9.0 g), obtained as described in Examples 27(a) or (c) respectively, is dissolved in ethanol (90 ml) and sodium borohydride (10.0 g) is added. The mixture is refluxed for 16 hours, the solvent evaporated under reduced pressure, and the residue is distributed between water and benzene. The benzene phase is dried with sodium carbonate, and evaporated to give 2-ethyl-1,2,3,7,8,12b-hexahydro-benzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, identical in all respects with a sample prepared as described in Example 17(d). The same compound is also obtained when using lithium aluminum hydride in tetrahydrofuran instead of sodium borohydride as above.

In the same manner, by using as starting material 11-chloro-2-methyl- and 11-chloro-2-ethyl-1,7,8,12b-tetrahydro-benzo[6,7]cyclohepta[1,2,3-d,e]isoquinolinium iodide, obtained as described in Example 27(d), there are obtained 11-chloro-2-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline, NMR ($CDCl_3$) 149 Hz ($NCH_3$), 400-460 Hz (aromatic), hydrochloride salt prepared with ethereal hydrogen chloride, m.p. 230-240°C (from isopropanol-ether), and 11-chloro-2-ethyl-1,2,3,7,8,21b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, NMR ($CDCl_3$) 187 Hz ($NCH_3$), 79 Hz($-CH_3$), 400-440 Hz (aromatic), hydrochloride salt prepared as above, m.p. 250-255°C (from isopropanol-ether).

In the same manner, by using as starting material any of the quaternary Schiff base salts obtained as described in Example 27 and treating with sodium borohydride or with lithium aluminum hydride, the correspondingly substituted derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline are obtained, identical with the same compounds obtained as described in Examples 17 and 24 are obtained.

(b) One equivalent of 2-methyl-1,7,8,12b-tetrahydrobenzo-[6,7]cyclohepta[1,2,3-d,e]isoquinolinium iodide, obtained as described in Example 27(c) is added in small portions with stirring to an ethereal solution of two equivalents of methyl magnesium bromide. The mixture is refluxed for one hour, cooled, saturated aqueous ammonium chloride is added, the ether layer separated, washed with water, dried over anhydrous magnesium sulfate, and evaporated, to yield 2,3-dimethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline, m.p. 104°C after crystallization from hexane, also characterized as the hydrochloride salt with m.p. 272°C after crystallization from chloroform-ether.

In the same manner, by using ethyl, propyl, isopropyl, butyl, isobutyl, amyl, isoamyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, allyl, methoxymethyl, cyclopropyl, cyclohexylmethyl, phenyl, or benzyl magnesium bromide and 2-methyl or 2-ethyl-1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinolinium iodide, the following derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline are obtained:

| | | |
|---|---|---|
| 2-methyl-3-ethyl-, | m.p. 86-87°C (hexane) | Hydrochloride m.p. 210-212°C (acetone-h xane) |
| 2-methyl-3-propyl-, | NMR($CDCl_3$):158 Hz ($NCH_3$), 130-140 Hz ($-CH_3$-, $-CH_2$) | Hydrochloride m.p. 217-220°C (methanol-hexane) |
| 2-methyl-3-isopropyl-, | NMR($CDCl_3$):158 Hz($NCH_3$), 39 Hz and 63 Hz ($-CH_3$) | Maleate m.p. 185° (ethanol) |
| 2-methyl-3-n-butyl-, | m.p. 68° (hexane) | Hydrochloride m.p. 214-216°C (acetone-hexane) |
| 2-methyl-3-isobutyl-, | NMR($CDCl_3$):155 Hz($NCH_3$), 34 and 60 Hz ($-CH_3$) | Maleate m.p. 163-166°C (acetone-ether) |
| 2-methyl-3-amyl-, | NMR($CDCl_3$):152 Hz($NCH_3$), 52 Hz ($-CH_3$), 80 Hz($-CH_2$) | Hydrochloride m.p. 188-190°C (hexane-ethyl acetate) |
| 2-methyl-3-isoamyl-, | NMR($CDCl_3$):156 Hz($NCH_3$), 53 Hz ($-CH(CH_3)_2$) | Hydrochloride m.p. 199-200°C (acetone-ether) |
| 2-methyl-3-n-hexyl-, | NMR($CDCl_3$):153 Hz($NCH_3$), 52 Hz($-CH_3$), 76 Hz($-CH_2$-) | Hydrochloride m.p. 161-165°C (ethyl acetate) |
| 2-methyl-3-n-heptyl-, | NMR($CDCl_3$):154 Hz($NCH_3$), 53 Hz ($-CH_3$) 76 Hz($-CH_2$-) | Hydrochloride m.p. 140-141°C (acetone) |
| 2-methyl-3-n-octyl-, | NMR($CDCl_3$):155 Hz($NCH_3$) 54 Hz($-CH_3$) 77 Hz($-CH_2$-) | Hydrochloride m.p. 144-145°C (acetone) |
| 2-methyl-3-n-nonyl-, | NMR($CDCl_3$):155 Hz($NCH_3$), 54 Hz($-CH_3$), 76 Hz($-CH_2$-) | Hydrochloride m.p. 126-129°C (acetone-ether) |
| 2-methyl-3-n-decyl-, | NMR($CDCl_3$):155 Hz($NCH_3$), 53 Hz($CH_3$), 76 Hz($-CH_2$-) | Hydrochloride m.p. 154°C (acetone-hexane) |
| 2-methyl-3-allyl-, | NMR($CDCl_3$):156 Hz($NCH_3$), 285-380 Hz (-CH=CH-) | Hydrochloride m.p. 214-215°C(ethyl acetate-hexane) |
| 2-methyl-3-cyclo-propyl-, | NMR($CDCl_3$): 163 Hz($NCH_3$), 40-70 Hz(cyclopropyl) | Hydrochloride m.p. 274-276°C (isopropanol-ether) |
| 2-methyl-3-phenyl-, | NMR($CDCl_3$):137 Hz($NCH_3$), 432 Hz (aromatic) | Hydrochloride m.p. 279-281°C (methanol-ether) |
| 2-ethyl-3-methyl-, | m.p. 96°C (hexane) | |
| 2,3-diethyl-, | m.p. 59°C (petroleum-ether) | |

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In the same manner by using methoxymethyl, cyclohexylmethyl, r benzyl magn sium bromide, th 3-methoxym thyl, 3-cyclohexylmethyl, and 3-benzyl derivatives of 2-methyl- and 2-ethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline are also obtained.

In the same manner, by using the Grignard reagents listed above and reacting them with the 6- or 9, 5- or 10-, 4- or 11-, or 12-methyl, 9,12-dimethyl, 4- or 11-t-butyl, 6- or 9-, 5- or 10- or 4- or 11-chloro, 4- or 11-fluoro, 4- or 11-bromo, 4,10- or 5,11-dibromo, 5- or 10-hydroxy or 4- or 11-hydroxy, 5- or 10-methoxy or 4- or 11-methoxy, 5- or 10-acetoxy, 4- or 11-methylthio, 4- or 11-methylsulfonyl, 4- or 11-trifluoromethyl, 12-amino, 12-methylamino, 4- or 11-dimethylaminosulfonyl, 4-bromo-11-dimethylaminosulfonyl or 11-bromo-4-dimethylaminosulfonyl, 4,11-dinitro and 4,9- or 6,11-dinitro derivatives of 1,7,8,12b-tetrahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolinium salts obtained as described in Example 27 or with their 1-methyl derivatives or with their 2-methyl, 2-ethyl, 2-allyl, 2-cyclopentyl, 2-cyclohexylmethyl, or 2-benzyl derivatives or their 1-methyl derivatives, the correspondingly substituted 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinolines are obtained.

EXAMPLE 29

1,2,3,7,8,12b-Hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (5.0 g), obtained as described in Examples 17, 19 or 24 is refluxed over night with 10 ml of benzyl chloride in the presence of 10 g of sodium carbonate in 100 ml of ethanol. After filtration of the inorganic solids and removal of solvent, the residual oil is dissolved in benzene and filtered through silica gel to yield 2-benzyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, NMR($CDCl_3$) 320 Hz ($CH_2$), 436 Hz (aromatic benzyl). The hydrochloride salt is prepared with ethereal hydrogen chloride and has m.p. 228°C after crystallization from isopropanol-ether.

In the same manner, by using methyl iodide, ethyl bromide, isopropyl bromide or propargyl bromide, the following derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinoline are obtained:

| | | |
|---|---|---|
| 2-Methyl-, | m.p. 90-91°C, (hexane) | hydrochloride m.p. 268-272°C (methanol-ether) |
| 2-Ethyl-, | m.p. 58.5 -60°C, (ethanol) | hydrochloride m.p. 238°C (isopropanol) |
| 2-Isopropyl-, | m.p. 67°C (ether) | maleate m.p. 159°C (isopropanol) |
| 2-Propargyl-, | m.p. 121°C (hexane) | hydrochloride m.p. 224°C (ethanol) |

In the same manner, by using allyl, cyclopentyl or cyclohexylmethyl chloride, bromide, or iodide, the corresponding 2-allyl, 2-cyclopentyl, and 2-cyclohexylmethyl derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline are also obtained.

In the same manner, by using as starting material the 1-methyl derivative of the above starting material, or the 3-methyl, 3-ethyl, 3-propyl, 3-isopropyl, 3-butyl, 3-isobutyl, 3-amyl, 3-isoamyl, 3-n-hexyl, 3-n-heptyl, 3-n-octyl, 3-n-nonyl, 3-n-decyl, 3-allyl, 3-methoxymethyl, 3-cyclopropyl, 3-cyclohexylmethyl, 3-phenyl, or 3-benzyl derivatives, or the 6- or 9, 5- or 10-, 4- or 11-, or 12-methyl, 9,12-dimethyl, 4- or 11-t-butyl, 6- or 9-, 5- or 10- or 4- or 11-chloro, 4- or 11-fluoro, 4- or 11-bromo, 4,10- or 5,11-dibromo, 5- or 10-hydroxy or 4- or 11-hydroxy, 5- or 10-methoxy or 4- or 11-methoxy, 5- or 10-acetoxy, 4- or 11-methylthio, 4- or 11-methylsulfonyl, 4- or 11-trifluoromethyl, 12-amino, 12-methylamino, 4- or 11-dimethylaminosulfonyl, 4-bromo-11-dimethylaminosulfonyl or 11-bromo-4-dimethylaminosulfonyl, 4,11-dinitro and 4,9- or 6,11-dinitro derivatives thereof, and reacting them with methyl, ethyl, allyl, cyclopentyl, cyclohexylmethyl, or benzyl chloride, bromide, or iodide in the manner described above, the 2-methyl, 2-ethyl, 2-allyl, 2-cyclopentyl, 2-cyclohexylmethyl, and 2-benzyl derivatives of the above compounds are respectively obtained.

EXAMPLE 30

(a) 1,2,3,7,8,12b-Hexahydrobenzo[6,7]cycl hepta[1,2,3-d,e]-isoquinoline (3.2 g) is added with stirring and cooling to a mixture of formic acid (2.5 ml) and acetic anhydride (5.8 ml) which had previously been heated at 60°C for 2 hours. The mixture is kept at room temperature for 24 hours, then poured onto ice and water, neutralized with sodium carbonate solution and extracted with chloroform. The chloroform phase is dried, evaporated to dryness, and the remaining residue is crystallized from a benzene-hexane mixture to give 2-formyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, m.p. 134-135°C.

1,2,3,7,8,12b-Hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (9.4 g) is kept for 24 hours in a mixture of pyridine (50 ml) and acetic anhydride (40 ml). Addition of water and extraction with chloroform gives 2-acetyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, m.p. 124-126° when crystallized from acetone.

By working in the manner described above, but using propenoic anhydride, propynoic anhydride, cyclohexylcarbonyl chloride, or benzoyl chloride instead of acetic anhydride, there are obtained 2-propenoyl-, 2-propynoyl-, 2-cyclohexyl-carbonyl-, and 2-benzoyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]-cyclohepta[1,2,3-d,e]isoquinoline .

(b) 2-Formyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinoline (5.0 g) prepared as described above, is added dropwise to a mixture of lithium aluminum hydride (2.5 g)

in eth r (200 ml) and the mixture is refluxed for 4 hours. Additions of water followed by washing, drying, and evaporating the ether phase yields 2-methyl-1,2,3,7,8,12b-hexahydrobenzo-[6,7]cyclohepta[1,2,3-d,e]isoquinoline, identical in all respects with the compound described in Example 17(d).

2-Acetyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta-[1,2,3-d,e]isoquinoline (3.6 g) prepared as described in Example 8, is stirred, under nitrogen, with a 1 M solution of diborane in tetrahydrofuran (30 ml) for 16 hours, then 20% aqueous hydrogen chloride (100 ml) is added and the tetra-hydrofuran is evaporated under reduced pressure. The mixture is made alkaline with 10% sodium hydroxide solution, and extracted with chloroform. The chloroform phase is washed with water, dried and evaporated. Crystallization of the residue from ethanol gives 2-ethyl-1,2,3,7,8,12b-hexahydro-benzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, m.p. 58.5-60°C, identical with the same compound described in Example 17(d).

2-Acetyl-1,2,3,7,8,12b-hexahydrobenzo[1,2]cyclohepta-[3,4,5-d,e]isoquinoline (10.0 g) is refluxed for 24 hours with lithium aluminum hydride (10.0 g) in 400 ml of tetra-hydrofuran. Addition of water followed by washing, drying and evaporating the organic phase yields the 2-ethyl derivative identical in all respects with the compound prepared as described above.

In the same manner, when using as starting material 2-propenoyl-, 2-propynoyl-, 2-cyclohexylcarbonyl-, or 2-benzoyl-

1,2,3,7,8,12b-hexahydrobenzo[6,7]cycloh pta[1,2,3-d,e]isoquinoline, obtained as described in Example 30(a), and treating with diborane or lithium aluminum hydride there are obtained 2-allyl-, 2-propargyl-, 2-hydrohexylmethyl-, and 2-benzyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, respectively.

(c) 1,2,3,7,8,12b-Hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (7.05 g) is dissolved in 8 ml of ethylene dichloride. 1N sodium hydroxide (33 ml) is added and to the vigorously stirred mixture, at 0°C, is added ethyl chloroformate (3.6 g) in 45 ml of ethylene dichloride. The mixture is stirred at room temperature for 90 minutes, then the organic phase is separated, washed with water, dried and evaporated. The resulting residue is crystallized from hexane to give 2-carbethoxy-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, m.p. 92-98°C.

2-Carbethoxy-1,2,3,7,8,12b-hexahydrobenzo[12,]cyclohepta[3,4,5-d,e]isoquinoline (3.0 g) prepared as described above, is added to a mixture of tetrahydrofuran (100 ml) and lithium aluminum hydride (3.0 g). The mixture is refluxed for 24 hours. Additions of water followed by washing, drying and evaporating the organic phase yields 2-methyl-1,2,3,7,8,12b-hexahydrobenzo-[6,7]cyclohepta[1,2,3-d,e]isoquinoline, identical in all respects with the compound described in Example 17(d).

(d) 1,2,3,7,8,12b-Hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline (10.0 g) is added to a mixture of formic acid (10 ml), 36% aqueous formaldehyde (10 ml) and water (10 ml). The

mixture is heated on a steam bath for 2 hours, then wat r (100 ml) is added, then ammonium hydroxide, until the reaction mixture is alkaline. Extraction with chloroform followed by washing, drying and evaporating the chloroform phase yields a residue. Crystallization from hexane gives 2-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, identical with the same compound described in Example 17(d).

By working in the same manner as described above, but using acetaldehyde instead of formaldehyde, 2-ethyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline is obtained, identical in all respects with the compound described in Example 17(d).

Alternatively, 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline (9.4 g) and acetaldehyde (5.0 g) are combined with ethanol (100 ml) and platinum oxide (0.5 g) and shaken with hydrogen at 60°C and 30 p.s.i. for four hours. Filtration and evaporation of the solvent yields the 2-ethyl derivative identical in all respects with the compound identified above.

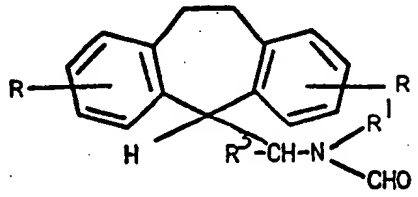
By working in the same manner as that described above, but using formaldehyde instead of acetaldehyde there is obtained 2-methyl-1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]-isoquinoline, identical with the compound described in Example 17 (d)

In the same manner, by using as starting material the 1-methyl and/or 3-methyl, 3-ethyl, 3-propyl, 3-isopropyl, 3-butyl,

3-isobutyl, 3-amyl, 3-isoamyl, 3-hexyl, 3-heptyl, 3-octyl, 3-nonyl, 3-decyl, 3-allyl, 3-methoxymethyl, 3-cyclopropyl, 3-cyclohexylmethyl, 3-phenyl, 3-benzyl and/or 6- or 9, 5- or 10-, 4- or 11-, or 12-methyl, 9,12-dimethyl, 4- or 11-t-butyl, 6- or 9-, 5- or 10- or 4- or 11-chloro, 4- or 11-fluoro, 4- or 11-bromo, 4,10- or 5,11-dibromo, 5- or 10-hydroxy or 4- or 11-hydroxy, 5- or 10-methoxy or 4- or 11-methoxy, 5- or 10-acetoxy, 4- or 11-methylthio, 4- or 11-methylsulfonyl, 4- or 11-trifluoromethyl, 12-amino, 12-methylamino, 4- or 11-dimethylaminosulfonyl, 4-bromo-11-dimethylaminosulfonyl or 11-bromo-4-dimethylaminosulfonyl, 4,11-dinitro and 4,9- or 6,11-dinitro derivatives of 1,2,3,7,8,12b-hexahydrobenzo[6,7]cyclohepta[1,2,3-d,e]isoquinoline, and reacting them with the alkylating or acylating agents or with the aldehydes described above, there are obtained the 2-methyl, 2-ethyl, 2-allyl, 2-propargyl, 2-cyclohexylmethyl and 2-benzyl derivatives of the compounds listed above, respectively.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

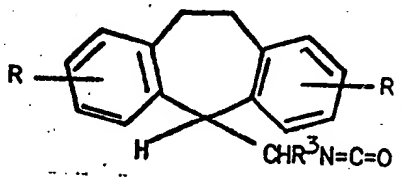
1. A process for preparing a compound of formula




XXVIIa

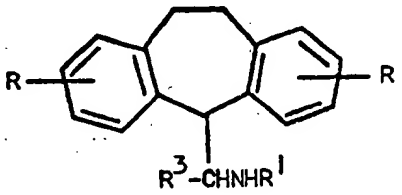
in which R represents one or more substituents, either the same or different from each other, selected from the group consisting of hydrogen and halo; $R^1$ is hydrogen; and $R^3$ is hydrogen or lower alkyl, which comprises:

(a) reacting an isocyanate of formula XXIV




XXIV

in which R and $R^3$ are as defined herein with a mineral acid to obtain the corresponding amine of formula IX in the form of its corresponding acid addition salt; treating said last-named acid addition salt with alkali, to obtain the corresponding amine of formula IX



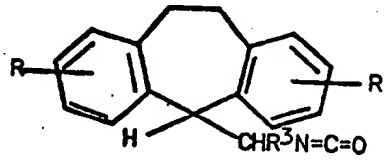

IX

B

in which R and $R^3$ are as defined herein and $R^1$ is hydrogen; and reacting said amine with a formylating ag nt to obtain the corresponding compound of formula XXVIIa in which R and $R^3$ are as defined herein and $R^1$ is hydrogen; or

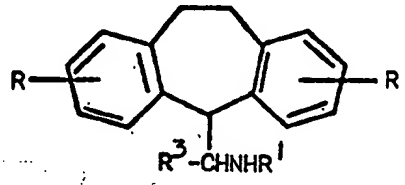
(b) reacting an isocyanate of formula XXIV in which R and $R^3$ are as defined herein with formic acid to obtain the corresponding compound of formula XXVIIa in which R and $R^3$ are as defined herein and $R^1$ is hydrogen.

2. The process of Claim 1 for preparing a compound of formula XXVIIa of Claim 1 wherein R, $R^1$ and $R^3$ are as defined therein, which comprises reacting an isocyanate of formula XXIV




XXIV

in which R and $R^3$ are as defined herein with a mineral acid to obtain the corresponding amine of formula IX in the form of its corresponding acid addition salt; treating said last-named acid addition salt with alkali, to obtain the corresponding amine of formula IX



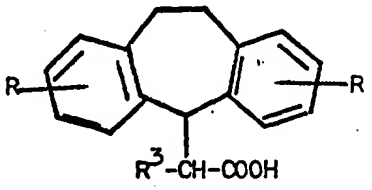

IX

in which R and $R^3$ are as defined herein and $R^1$ is hydrogen; and reacting said amine with a formylating agent to obtain the corresponding compound of formula XXVIIa in which R and $R^3$ are as defined herein and $R^1$ is hydrogen.

B

3. The process of Claim 1 for preparing a compound of formula XXVIIa of Claim 1 wherein R, $R^1$ and $R^3$ are as defined therein, which comprises reacting an isocyanate of formula XXIV of Claim 1 in which R and $R^3$ are as defined herein with formic acid to obtain the corresponding compound of formula XXVIIa in which R and $R^3$ are as defined herein and $R^1$ is hydrogen.

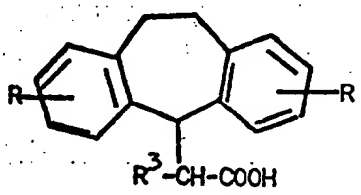
4. The process of Claim 2 wherein the isocyanate of formula XXIV is prepared by a process comprising reacting a 5-alkanoic acid of formula XV




XV

in which R and $R^3$ are as defined therein with a halogenating agent to obtain the corresponding acid halide; treating said acid halide with an alkali metal azide, to obtain the corresponding acid azide; and heating said acid azide to obtain the corresponding isocyanate of formula XXIV.

5. The process of Claim 3 wherein the isocyanate of formula XXIV is prepared by a process comprising reacting a 5-alkanoic acid of formula XV

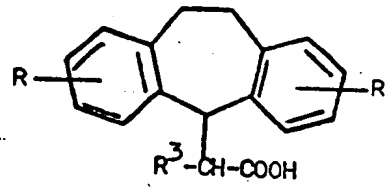



XV

in which R and $R^3$ are as defined therein with a halogenating agent to obtain the corresponding acid halide; treating said acid halide with an alkali metal azide, to obtain the corresponding acid azide; and heating said acid azide to obtain the corresponding isocyanate of formula XXIV.

B

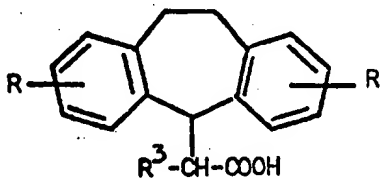
6. The process of Claim 2 wherein the isocyanate of formula XXIV is prepared by a process comprising reacting a 5-alkanoic acid of formula XV



XV

in which R and $R^3$ are as defined therein, or its corresponding acid halide or its corresponding methyl ester with hydrazine hydrate to obtain the corresponding acid hydrazide; treating said last-named hydrazide with an alkali metal nitrite in the presence of an acid to obtain the corresponding acid azide; and heating said acid azide to obtain the corresponding isocyanate of formula XXIV.

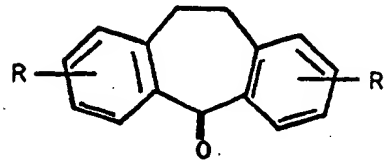
7. The process of Claim 3 wherein the isocyanate of formula XXIV is prepared by a process comprising reacting a 5-alkanoic acid of formula XV



XV

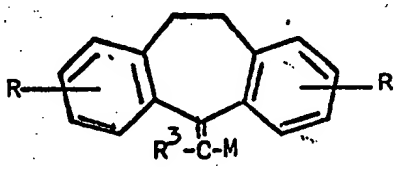
in which R and $R^3$ are as defined therein, or its corresponding acid halide or its corresponding methyl ester with hydrazine hydrate to obtain the corresponding acid hydrazide; treating said last-named hydrazide with an alkali metal nitrite in the presence of an acid to obtain the corresponding acid azide; and heating said acid azide to obtain the corresponding isocyanate of formula XXIV.

8. The process of Claim 4 or 5 wher in the 5-alkanoic acid of formula XV in which R and $R^3$ are as defined therein is prepared by a process comprising reacting a compound of formula II



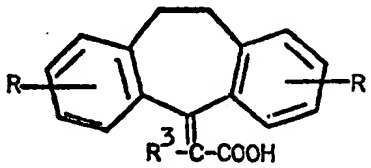
II

in which R is as defined therein with a di-(lower alkyl)phosphono-alkanoic acid lower alkyl ester of the formula (lower alkyl-O)$_2$P-(→O)CHR$^3$M in which $R^3$ is as defined in the first instance and M is the group COO-(lower alkyl) in the presence of a base to obtain the corresponding ylidenealkanoic acid lower alkyl ester of the formula XIII



XIII

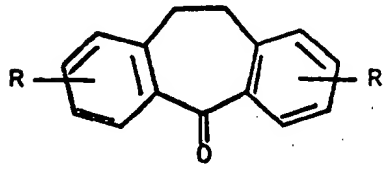
in which R, $R^3$, and M are as defined herein; treating said compound of formula XIII with a mineral acid or with an alkali metal hydroxide to obtain the corresponding 5-ylidenealkanoic acid of formula XI



XI

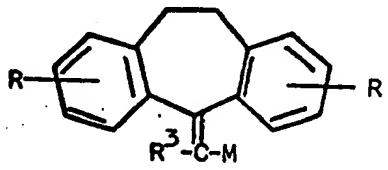
in which R and $R^3$ are as defined herein; and treating said 5-ylidenealkanoic acid of formula XI with a reducing agent to obtain the corresponding 5-alkanoic acid of formula XV.

9. The process of Claim 6 or 7 wher in th 5-alkanoic acid of formula XV in which R and $R^3$ ar as defined therein is prepared by a process comprising reacting a compound of formula II



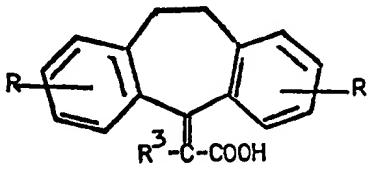
II

in which R is as defined therein with a di(lower alkyl)phosphono-alkanoic acid lower alkyl ester of the formula (lower alkyl-O)$_2$P(→O)CHR$^3$M in which $R^3$ is as defined in the first instance and M is the group COO(lower alkyl) in the presence of a base to obtain the corresponding ylidenealkanoic acid lower alkyl ester of the formula XIII



XIII

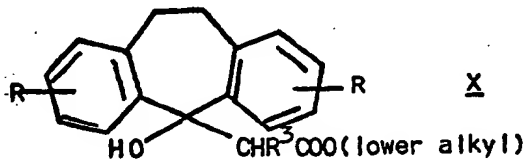
in which R, $R^3$, and M are as defined herein; treating said compound of formula XIII with a mineral acid or with an alkali metal hydroxide to obtain the corresponding 5-ylidenealkanoic acid of formula XI



XI

in which R and $R^3$ are as defined herein; and treating said 5-ylidenealkanoic acid of formula XI with a reducing agent to obtain the corresponding 5-alkanoic acid of formula XV.

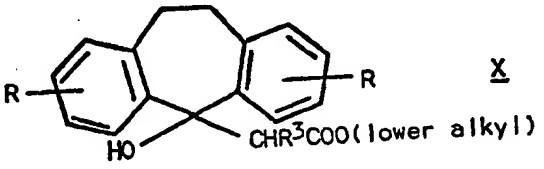
10. The process of Claim 4 or 5 wherein the 5-alkanoic acid of formula XV in which R and $R^3$ are as defined ther in is prepared by a process comprising reacting a compound of formula II in which R is as defined therein with a lower alkyl ester of an α-haloalkanoic acid of the formula $XCHR^3COO$(lower alkyl) in which X is a halogen with an atomic weight greater than 19 and $R^3$ is as defined herein in the presence of zinc metal, to obtain the corresponding 5-hydroxy-5-alkanoic acid lower alkyl ester of formula X




X

in which R and $R^3$ are as defined herein; treating said lower alkyl ester of formula X with a mineral acid to obtain the corresponding 5-ylidenealkanoic acid of formula XI in which R and $R^3$ are as defined herein; and treating said 5-ylidene-alkanoic acid of formula XI with a reducing agent to obtain the corresponding 5-alkanoic acid of formula XV.

11. The process of Claim 6 or 7 wherein the 5-alkanoic acid of formula XV in which R and $R^3$ are as defined therein is prepared by a process comprising reacting a compound of formula II in which R is as defined therein with a lower alkyl ester of an α-haloalkanoic acid of the formula $XCHR^3COO$(lower alkyl) in which X is a halogen with an atomic weight greater than 19 and $R^3$ is as defined herein, in the presence of zinc metal, to obtain the corresponding 5-hydroxy-5-alkanoic acid lower alkyl ester of formula X




X

B

in which R and $R^3$ are as defined herein; treating said lower alkyl ester of formula X with a mineral acid to obtain the corresponding 5-ylidenealkanoic acid of formula XI in which R and $R^3$ are as defined herein; and treating said 5-ylidenealkanoic acid of formula XI with a reducing agent to obtain the corresponding 5-alkanoic acid of formula XV.

12. The process of Claim 1 or 2 wherein the mineral acid is hydrochloric acid and the formylating agent is selected from the group consisting of formic acetic anhydride, chloral, formic acid, and a lower alkyl formate.

13. The process of Claim 4 or 5 wherein the halogenating agent is thionyl chloride and the alkali metal azide is sodium azide.

14. The process of Claim 6 or 7 wherein the alkali metal nitrite is sodium nitrite.

15. The process of Claim 1, wherein R and $R^3$ both are hydrogen.

16. The process of Claims 2, 3 or 4 wherein R and $R^3$ both are hydrogen.

17. The process of Claims 5, 6 or 7 wherein R and $R^3$ are both hydrogen.

18. The process of Claim 1 wherein R is chloro and $R^3$ is hydrogen.

19. The process of Claims 2, 3 or 4 wherein R is chloro and $R^3$ is hydrogen.

20. The process of Claims 5, 6 or 7 wherein R is chloro and $R^3$ is hydrogen.

# SUBSTITUTE

# *REMPLACEMENT*

## SECTION is not Present

## *Cette Section est Absente*